KYTRIL VS. ZOFRAN

Assumptions

	70 KG PATIENT
Body Weight (lbs)	154
Zofran Price	$168.00
Kytril Price	$120.00

# Doses Annually	ZOFRAN 32MG $ Volume	ZOFRAN .15mg/kgx3 $ Volume	KYTRIL 10 mcg/kg $ Volume	32MG VS 10MCG/KG Savings 37.5%
1	$134	$132	$84	$50
30	$4,032	$3,969	$2,520	$1,512
60	$8,064	$7,938	$5,040	$3,024
90	$12,096	$11,907	$7,560	$4,536
120	$16,128	$15,876	$10,080	$6,048
150	$20,160	$19,845	$12,600	$7,560
200	$26,880	$26,460	$16,800	$10,080
250	$33,600	$33,075	$21,000	$12,600
300	$40,320	$39,690	$25,200	$15,120
350	$47,040	$46,305	$29,400	$17,640
400	$53,760	$52,920	$33,600	$20,160
450	$60,480	$59,535	$37,800	$22,680
500	$67,200	$66,150	$42,000	$25,200
550	$73,920	$72,765	$46,200	$27,720
600	$80,640	$79,380	$50,400	$30,240
1200 DOSES/YEAR (23 doses/week)	$160,800 -100,800	$158,400 -100,800	$100,800	
KYTRIL SAVINGS	$60,000	$57,600		

TIME SAVED IN NURSING HOURS: INFUSION TIME COMPARISON

KYTRIL = 5 MINUTES — ZOFRAN = 15 MINUTES

1200 doses/year = 6000 minutes — 1200 doses/year = 18,000 minutes

THE KYTRIL SHORTER INFUSION TIME TRANSLATES INTO A SAVINGS OF 12,000 MIN OR 200 NURSING HOURS SAVED BY ADMINISTERING KYTRIL INSTEAD OF ZOFRAN.

CONCLUSION: KYTRIL IS AS EFFECTIVE AS ZOFRAN, IS EASIER TO ADMINISTER, AND IS SIGNIFICANTLY MORE COST EFFECTIVE!

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Kytril vs. ondansetron

an 'Apples to Apples' comparison of the 5HT-3 antagonists' costs

	Kytril[1]	ondansetron
Vial[2]	1mg/mL	40mg/20mL
Cost/vial[3]	120.35	172.92
scenario #1 Dosing at FDA approved amounts.		
Dose	0.7g[4]	32mg[5]
Cost/patient	84.25	138.34
Savings	54.09	-------
scenario #2 2/3 of the FDA approved doses of each drug.		
Dose	0.5mg	24mg
Cost/patient	60.18	103.75
Savings	43.57	-------
scenario #3 1/2 of the FDA approved doses of each drug.		
Dose	0.35mg	16mg
Cost/patient	42.13	69.17
savings	27.05	------

[1]all of Kytril's dosing is based on an average patient body weight of 70kg.
[2]for all calculations, these vial volumes are constant.
[3]based on average contracted pricing information for both drugs, also constant throughout these scenarios.
[4] 10mcg/kg Kytril for all patients.
[5]the only FDA -approved single dosing for ondansetron.

Additional benefits for Hospital Formulary consideration

1. No promotion or indication of Kytril for Post Operative Nausea and vomiting.

2. No promotion of Kytril for Delayed Onset Nausea and Vomiting.

3. Reduced Nursing administration costs--5 minute infusion time Kytril vs. 15 minute infusion time for ondansetron.

4. Kytril's 9 hour 1/2 life vs. ondansetron's 4 hour 1/2 life.

5. Price reduction on Compazine--see contract.

6. SmithKline Beecham will provide Kytril free of charge for indigent patients--see SB access to care application form.

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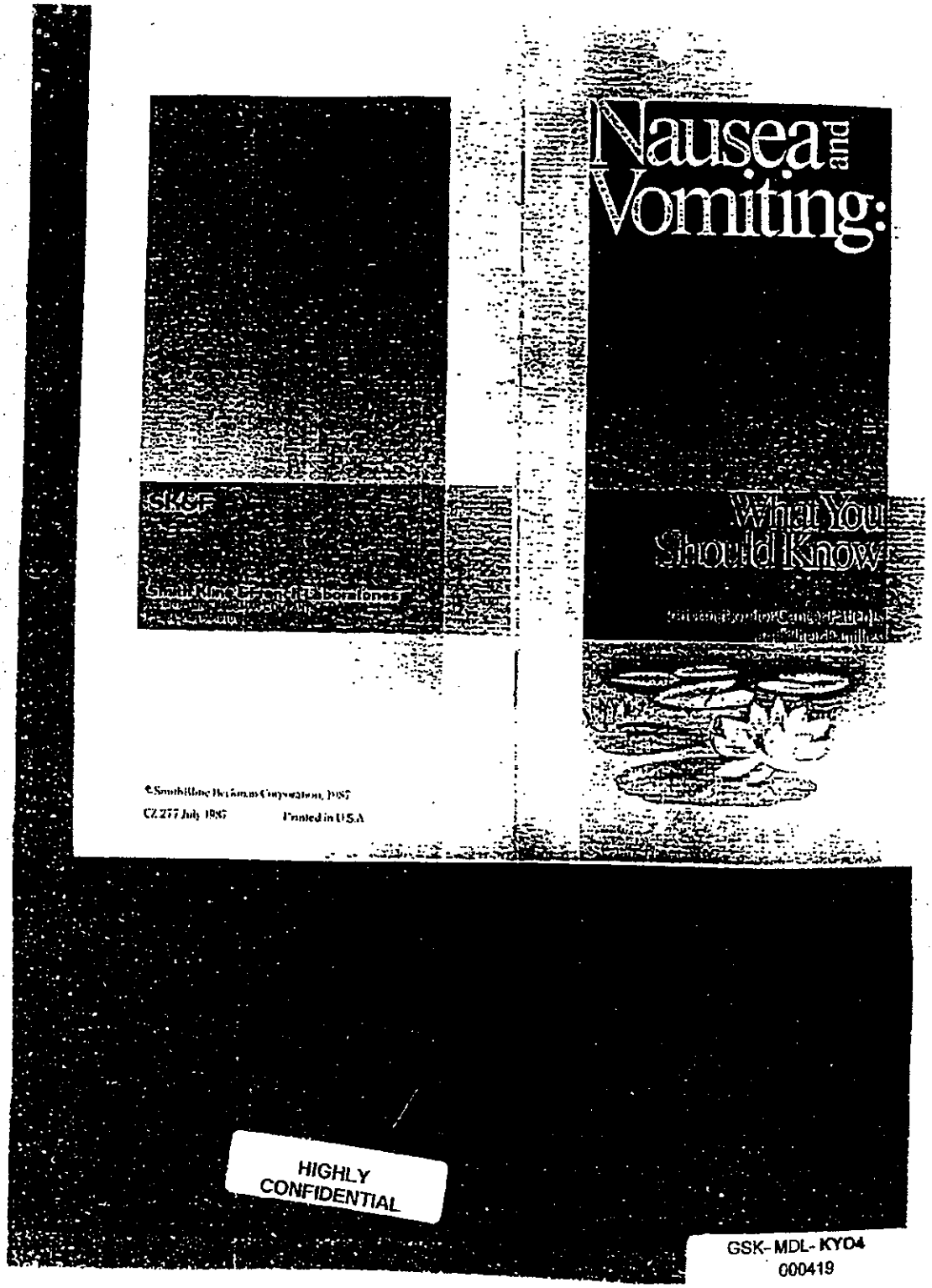
Nausea and Vomiting:
What You Should Know
SK&F
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What is nausea and vomiting?

You have probably had nausea before. Nausea is that "sick" or uncomfortable feeling in your stomach that often goes along with vomiting.

Vomiting, or "throwing up," is also something most people have experienced at some time.

Many cancer patients have nausea and/or vomiting at some time during their treatment. It is an unpleasant experience, but there are ways to reduce the number of times it occurs.

Why do nausea and vomiting occur?

Nausea and vomiting are ways that your body reacts to stress. The stress may be physical or emotional.

Examples of *physical* stress that can cause nausea and vomiting include common problems like eating or drinking too much or a bad case of the flu. More severe physical stress such as a broken bone or surgery often causes nausea and vomiting.

The physical stress of some forms of cancer can cause nausea and vomiting. And the therapy (drugs and/or radiation) creates an additional stress.

Everyone reacts to *emotional* stress in different ways. Some people cry, some get very angry, and others may get very nauseated or even vomit.

No one knows *exactly* how nausea and vomiting occur. We do know that there are two

different centers in the brain which can send out the signals that cause nausea and vomiting. And we know some of the things that act on these centers to make them send signals. We also know that some drugs can act on these centers to reduce, or stop, nausea and vomiting.

Some of the reasons cancer and cancer treatment cause nausea and vomiting include:

- certain chemotherapy agents which can trigger the vomiting center
- stimulation of the vomiting centers in the brain by chemicals released when cancer cells are destroyed by chemotherapy or radiation therapy
- radiation, which can cause nausea and vomiting through its direct effects on the esophagus, stomach, intestines and/or the head
- chronic pain
- fatigue associated with cancer treatment
- taste and smell changes
- negative past experiences associated with cancer therapy

Some cancer patients suffer nausea and vomiting just at the thought of having their drug treatments. This problem, known as "anticipatory nausea and vomiting," results from anxiety (emotional stress) about receiving treatments and the expectation (or *anticipation*) of being sick afterward.

What can I do if I experience nausea and vomiting?

The following suggestions have helped many people reduce the problem of nausea and vomiting. You will probably need to experiment to find what works best for you.

Remember, if vomiting is severe, call your physician or nurse.

How should I eat when I'm feeling nauseated?

- Eat small portions, slowly.
- Eat dry foods, such as toast or crackers.
- Drink liquids such as ginger ale, colas and fruit juices to reduce nausea. Also try clear soups, gelatin, tea and popsicles. Sip slowly.
- Eat cold or room temperature foods such as sandwiches, cereals, salads and desserts.

What should I avoid?

- spicy foods (pizza, chili, etc.).
- fatty, fried or greasy foods (french fries, butter, cheese, etc.).
- red meats (foods that are hard to digest are more likely to upset your stomach).
- foods with a strong odor. Your sense of smell can trigger an attack of nausea and vomiting.

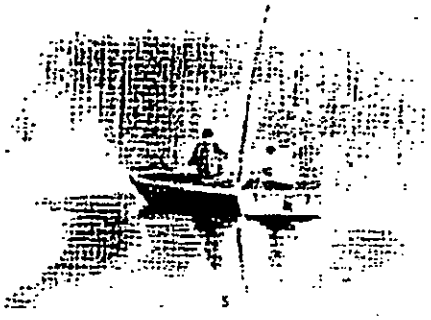
- your favorite foods. If the foods you like best become associated with nausea, you may not be able to eat them when you are feeling well.

What should I eat on the day of my chemotherapy treatment?

- Eat light meals.
- Avoid foods that are fatty (for example, fried foods or dairy products) or have a lot of acid (orange juice, salads with vinegar, etc.).
- Try not to eat or drink anything for 1-2 hours before and after your treatment.

Should I try to eat or drink anything if I am vomiting?

No. Do not try to eat or drink anything while you are vomiting or for several hours afterward. When you are feeling better, start with small sips of liquids.



What else can I do?

In addition to adjusting your diet to help reduce nausea and vomiting, there are also many other ways for you to manage these side effects.

- Avoid lying flat immediately after eating. Keep your head elevated at least 4 inches.
- Limit unpleasant odors, sights and sounds that may aggravate nausea.
- Remove dentures, retainers or any other foreign objects prior to receiving treatment.
- If taste changes occur in your mouth, suck on hard candy, such as a peppermint.
- If possible, open a window, allowing fresh air to circulate.
- Breathe through your mouth during times of severe nausea, until the feeling passes.
- Rinse your mouth out frequently to avoid unpleasant, sour taste.
- Avoid excessive activity and sudden movements that may interfere with your sense of balance.
- Allow adequate rest periods between your normal activities.
- Try to sleep through times of increased nausea, if you can.
- Take part in diversional activities, such as TV, games, music, handwork or conversation.
- Have a friend or family member stay with you for support and reassurance.
- Learn methods to control your nausea such as relaxation techniques, guided visual imagery and hypnosis. These measures, which focus on muscle relaxation and images of pleasant places and thoughts, can be started with the assistance of your nurse or physician.

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Are there medications that can help?

Yes. Drugs called antiemetics (*anti*=against and *emetic*=things that cause vomiting) are used to control or minimize nausea and vomiting. There are a variety of these medications available to treat nausea and vomiting.

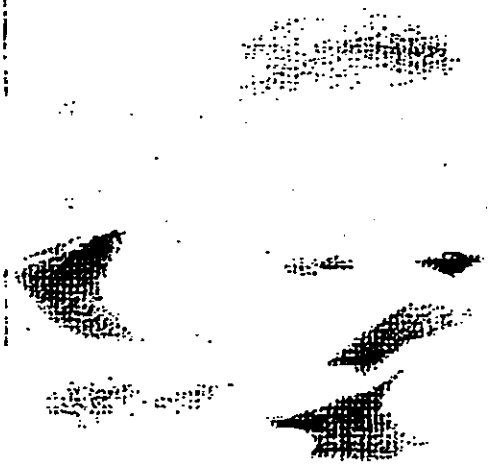
Antiemetics work by blocking or inhibiting messages from reaching the parts of the brain which control nausea and vomiting. Your doctor will choose which drug or combination of drugs is most appropriate for you, based on an individual evaluation and your planned therapy regimen.

Antiemetics are usually given before the start of a chemotherapy or radiation therapy session and continued at regularly prescribed intervals to be most effective. You should continue to take your antiemetic medication according to the schedule you are given, even if you feel fine. The need for antiemetic drugs may last for as long as two or three days following a chemotherapy treatment.

For convenience, sustained-release antiemetics (long-acting "time" capsules) can provide relief of nausea and vomiting for up to 12 hours. This may eliminate the need for taking medication more often. Your physician may also give you rectal suppositories of the same antiemetic to use if you are vomiting and a capsule is not likely to stay down.

Most antiemetics cause a mild sedation or tiredness, especially during the first few days of taking the drug. Activities such as driving a car should be avoided until your particular reaction to the drug can be determined.

If you work closely with the health care team throughout your cancer treatment, the most effective drugs, dose and administration schedule can be worked out to control the nausea and vomiting which may occur. Don't suffer silently. If your medication isn't working, let your treatment team know. They are there to help.



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DOSING & ADMINISTRATION COMPARISON

	KYTRIL (granisetron)	ZOFRAN (ondansetron)	
Half-Life	9hrs	4hrs	
Dose-adults	10mcg/Kg/day single dose	0.15mg/Kg at 0,4,8hrs or 32mg single dose	
Dose-pediatrics	10mcg/Kg/day single dose	0.15mg/Kg at 0,4,8hrs	
Dose-hepatically impaired	10mcg/Kg/day single dose	8mg single dose	
Dose-renally impaired	10mcg/Kg/day single dose	No data	
Infusion time	5 minutes	15 minutes	
Dilution	20-50ml of 5% dextrose or 0.9% saline.	50ml of 5% dextrose or 0.9% saline	
Stabilty when mixed	24hrs at room temperature.	Do not use beyond 24hrs.	
Vial size	1mg/1ml single dose	40mg/20ml multi-dose	
Dose used	10mcg/Kg single dose	0.15mg/Kg 3 dose	32mg single dose
15Kg(33lbs)	0.15mg	6.75mg	
30Kg(66lbs)	0.30mg	13.5 mg	
50Kg(110lbs)	0.50mg	22.5 mg	32mg
71Kg(157lbs)	0.71mg	32.0 mg	32mg
100Kg(220lbs)	1.0 mg	45.0 mg	32mg

COST COMPARISON
BASED ON ZOFRAN COST OF $172/40mg/20ml VIAL
KYTRIL COST OF $119/1mg/1ml VIAL

Patient Size	Kytril Cost 10mcg/Kg	Zofran Cost	
		0.15mg/Kgx3	32mg
15Kg(33lbs)	$17.85(.15mg)	$29.03(6.75mg)	
30Kg(66lbs)	$35.70(.30mg)	$58.06(13.5mg)	
50Kg(110lbs)	$59.50(.50mg)	$96.75(22.5mg)	$137.60
71Kg(157lbs)	$84.49(.71mg)*	$137.60(32mg)	$137.60
100Kg(220lbs)	119.00(1.0mg)	$193.50(45mg)	$137.60

*Cost Savings=38.6%

KYTRIL REIMBURSEMENT INFORMATION

KYTRIL J CODE - J 3490

REIMBURSEMENT QUESTIONS FOR KYTRIL - 1-800-699-3806

Most insurance companies, Medicare, and Medicaid will reimburse at 80% of the Actual Wholesale Price which is $166.00 for Kytril, or $132.80.

The unit if reimbursement is the 1mg/1ml single dose vial for all doses,(the 1mg/1ml single dose vial is enough for a 220 pound person)

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KYTRIL™

granisetron hydrochloride Injection

DOSAGE AND ADMINISTRATION

The recommended dosage for Kytril Injection is 10 mcg/kg infused intravenously over 5 minutes, beginning within 30 minutes before initiation of chemotherapy, and only on the day(s) chemotherapy is given.

kg.	lbs.	mcg.	ml
5	11	50	0.05
6	13	60	0.06
7	15	70	0.07
8	18	80	0.08
9	20	90	0.09
10	22	100	0.10
11	24	110	0.11
12	26	120	0.12
13	29	130	0.13
14	31	140	0.14
15	33	150	0.15
16	35	160	0.16
17	37	170	0.17
18	40	180	0.18
19	42	190	0.19
20	44	200	0.20
21	46	210	0.21
22	49	220	0.22
23	51	230	0.23
24	53	240	0.24
25	55	250	0.25
26	57	260	0.26
27	60	270	0.27
28	62	280	0.28
29	64	290	0.29
30	66	300	0.30
31	68	310	0.31
32	71	320	0.32
33	73	330	0.33
34	75	340	0.34
35	77	350	0.35
36	79	360	0.36
37	82	370	0.37
38	84	380	0.38
39	86	390	0.39
40	88	400	0.40
41	90	410	0.41
42	93	420	0.42
43	95	430	0.43
44	97	440	0.44
45	99	450	0.45
46	101	460	0.46
47	104	470	0.47
48	106	480	0.48
49	108	490	0.49
50	110	500	0.50
51	112	510	0.51
52	115	520	0.52
53	117	530	0.53

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54	119	540	0.54
55	121	550	0.55
56	123	560	0.56
57	126	570	0.57
58	128	580	0.58
59	130	590	0.59
60	132	600	0.60
61	134	610	0.61
62	137	620	0.62
63	139	630	0.63
64	141	640	0.64
65	143	650	0.65
66	146	660	0.66
67	148	670	0.67
68	150	680	0.68
69	152	690	0.69
70	154	700	0.70
71	157	710	0.71
72	159	720	0.72
73	161	730	0.73
74	163	740	0.74
75	165	750	0.75
76	168	760	0.76
77	170	770	0.77
78	172	780	0.78
79	174	790	0.79
80	176	800	0.80
81	179	810	0.81
82	181	820	0.82
83	183	830	0.83
84	185	840	0.84
85	187	850	0.85
86	190	860	0.86
87	192	870	0.87
88	194	880	0.88
89	196	890	0.89
90	198	900	0.90
91	201	910	0.91
92	203	920	0.92
93	205	930	0.93
94	207	940	0.94
95	209	950	0.95
96	212	960	0.96
97	214	970	0.97
98	216	980	0.98
99	218	990	0.99
100	220	1000	1.00

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Compatibility and Stability of 'Kytril' Injection with Intravenous Fluids

Compatibility and stability data for 'Kytril' Injection are presented below. Several intravenous (IV) fluids were tested using three infusion containers under varying storage conditions for up to 48 hours. In all cases, granisetron was diluted to a nominal concentration of 0.15 mg/ml.

The infusion (dilution) fluids used were as follows:

- 0.9% Sodium Chloride (normal saline, NSS)
- 5% Dextrose in Water (D_5W)
- 4% Dextrose/0.18% Saline
- Sodium Lactate Infusion
- Mannitol 10%
- Hartmann's Solution (Ringer's Lactate, Lactated Ringer's, Compound Sodium Lactate Solution)[4]

Infusion containers used included:

- Glass flasks
- Styrene acrylic nitrile syringe
- Polypropylene syringe

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Storage conditions tested:

- 5° C (dark)
- Ambient temperature, protected from light
- Ambient temperature in a mixture of daylight and ambient fluorescent light
- Cycled between 5° C (dark) and ambient temperature (fluorescent light)

Study results demonstrated that 'Kytril' Injection was physically compatible, ie, there were no changes in the appearance or pH of the solutions used, and chemically stable, ie, there was no change from the initial granisetron content after 48 hours, in the containers tested and under the above-mentioned storage conditions.

'Kytril' Injection should be used immediately after preparation. If proper precautions are taken to avoid microbiological contamination during mixing, a 24-hour shelf life may be assigned to diluted solutions.[5] This recommendation (24 hour stability), as previously mentioned, is stated in the enclosed prescribing information.

Compatibility and Stability of 'Kytril' Injection with Different Types of Infusion Equipment

In an attempt to evaluate the compatibility of 'Kytril' Injection with various types of infusion equipment, investigators placed solutions of granisetron in 0.9% saline in a PVC (polyvinyl chloride) infusion bag as well as in polypropylene syringes. The following table presents the concentrations of granisetron used, the types of syringes and PVC bag (along with the respective manufacturers), the length of the storage period and the appearance of the solutions and the granisetron content at the beginning and end of the study time.

Compatibility with Infusion Equipment

Container	Capacity	Granisetron content (nominal)	Storage period	Appearance	Granisetron content (% initial)
Polypropylene Syringe, ('Monoject', Model #560125, Sherwood Medical)	60 ml	0.40 mg/ml 0.04 mg/ml	Initial & 24 hrs Initial & 24 hrs	After 24 hrs, clear colorless solutions seen with both concentrations, as initially	100
Polypropylene Syringe ('Plastipak', Model #5663, Becton Dickinson)	50 ml	0.40 mg/ml 0.04 mg/ml	Initial & 24 hrs Initial & 24 hrs	After 24 hrs, clear colorless solutions seen with both concentrations, as initially	100
PVC infusion bag ('Viaflex' mini-bag, Travenol)	50 ml	0.40 mg/ml 0.04 mg/ml	Initial & 24 hrs Initial & 24 hrs	After 24 hrs, clear colorless solutions seen with both concentrations, as initially	100

As depicted in the above table, granisetron showed no evidence of chemical degradation or physical incompatibility following storage for 24 hours in plastic syringes or plastic infusion bags. Therefore, 'Kytril' Injection would remain physically compatible and chemically stable for 24 hours following storage in any of the above mentioned plastic containers.

Compatibility and Stability with Dexamethasone

In a study conducted by SmithKline Beecham Pharmaceuticals,[6] 'Kytril' Injection and dexamethasone sodium phosphate (two concentrations) were diluted with various volumes of 0.9% sodium chloride and glucose intravenous infusions and stored for 24 hours at 4° C and 30° C. The concentrations of active ingredients used were 'Kytril' Injection, 3 mg granisetron (as the hydrochloride) in 3 ml, dexamethasone sodium phosphate, 6.6 mg dexamethasone in

2 ml and dexamethasone sodium phosphate, 100 mg dexamethasone in 5 ml. As previously mentioned, the FDA approved dose of 'Kytril' in the U.S. is 10 mcg/kg.

The solutions were tested initially and then after 24 hrs at 4°C and 30°C. Granisetron was assayed by high-performance liquid chromatography (HPLC) for content and degradation profile using the current SmithKline Beecham registered methods[5] for 'Kytril' Injection. No interference was found from either dilution mediums. The dexamethasone content was determined using the methodology given in the USP XXII monograph for Dexamethasone Sodium Phosphate Injection. This HPLC method is specific for dexamethasone.

Solutions tested

Compatibility solution (Diluent)	Granisetron content	Dexamethasone content
1 ("maximum" concentration in saline)	3 mg/25 ml 0.9% Sodium chloride	100 mg/ 25 ml 0.9% Sodium chloride
2 ("minimum" concentration in saline)	3 mg/500 ml 0.9% Sodium chloride	6.6 mg/500 ml 0.9% Sodium chloride
3 ("maximum" concentration in glucose)	3 mg/25 ml Glucose Infusion	100 mg/25 ml Glucose Infusion
4 ("minimum" concentration in glucose)	3 mg/500 ml Glucose Infusion	6.6 mg/500 ml Glucose Infusion

Results from these tests demonstrated that 'Kytril' Injection and dexamethasone combinations are both physically and chemically stable when mixed in the concentration ranges tested in either 0.9% Sodium Chloride Intravenous Infusion, BP (British Pharmacopoeia) or in 5% Glucose Intravenous Infusion, BP, for up to 24 hours at 30°C, unprotected from light.[5]

NEW KYTRIL™ granisetron HCl Injection

One-dose convenience, 24-hour control

Cost Calculator

Current cost for ondansetron

32 mg × $ 4.45 /mg = 142.40

Dose | Cost/mg* | Cost per patient

(178.00 vial)

Current cost for *Kytril*

$ 120.35 = 120.35

Cost/vial* | Cost per patient

22.05 (15% Less Expensive)

Cost difference

*Based on actual purchase price specific to this institution

The most common side effects† in chemotherapy patients who received *Kytril* are headache (14%), asthenia (5%), somnolence (4%), diarrhea (4%) and constipation (3%)

†In the absence of a placebo group, there is uncertainty as to how many of these events should be attributed to *Kytril* except for headache.

NOTE TO PHARMACEUTICAL CONSULTANT: When this information is shown to physicians, complete prescribing information must be presented.

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Kytril vs. Zofran

Assumptions	45 kg
Body Weight (lbs)	100
Zofran Price	$180.00
Kytril Price	$128.00

Maximum Zofran dose cost-comparable to full Kytril dose: 12.7 mg

# Doses Annually	*Zofran* 32 mg $ Volume	*Zofran* .15 mg/kg x 3 $ Volume	*Kytril* 10 mcg/kg $ Volume	Savings 60.2%
1	$144	$92	$57	$87
30	$4,320	$2,761	$1,716	$2,602
60	$8,640	$5,523	$3,436	$5,204
90	$12,960	$8,284	$5,155	$7,805
120	$17,280	$11,045	$6,873	$10,407
150	$21,600	$13,807	$8,591	$13,009
200	$28,800	$18,409	$11,455	$17,345
250	$36,000	$23,011	$14,318	$21,682
300	$43,200	$27,614	$17,182	$26,018
350	$50,400	$32,216	$20,045	$30,355
400	$57,600	$36,818	$22,909	$34,691
450	$64,800	$41,420	$25,773	$39,027
500	$72,000	$46,023	$28,636	$43,364
550	$79,200	$50,625	$31,500	$47,700
600	$86,400	$55,227	$34,364	$52,036

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Kytril Cost	$118.03	Monthly Cost Savings	$780.78
Zofran Cost	$173.80	Annual Cost Savings	$9,369.36
Monthly Usage	28 VIALS		
Percent Kytril	50%		

Monthly Cost Savings

Usage/Month	20%	40%	60%	80%	100%
28	312.31	624.62	936.94	1,249.25	1,561.56
5	55.77	111.54	167.31	223.08	278.85
10	111.54	223.08	334.62	446.16	557.70
15	167.31	334.62	501.93	669.24	836.55
20	223.08	446.16	669.24	892.32	1,115.40
25	278.85	557.70	836.55	1,115.40	1,394.25
30	334.62	669.24	1,003.86	1,338.48	1,673.10
50	557.70	1,115.40	1,673.10	2,230.80	2,788.50
75	836.55	1,673.10	2,509.65	3,346.20	4,182.75
100	1,115.40	2,230.80	3,346.20	4,461.60	5,577.00

ANNUAL Cost Savings

Usage/Month	20%	40%	60%	80%	100%
28	3,747.74	7,495.49	11,243.23	14,990.98	18,738.72
5	669.24	1,338.48	2,007.72	2,676.96	3,346.20
10	1,338.48	2,676.96	4,015.44	5,353.92	6,692.40
15	2,007.72	4,015.44	6,023.16	8,030.88	10,038.60
20	2,676.96	5,353.92	8,030.88	10,707.84	13,384.80
25	3,346.20	6,692.40	10,038.60	13,384.80	16,731.00
30	4,015.44	8,030.88	12,046.32	16,061.76	20,077.20
50	6,692.40	13,384.80	20,077.20	26,769.60	33,462.00
75	10,038.60	20,077.20	30,115.80	40,154.40	50,193.00
100	13,384.80	26,769.60	40,154.40	53,539.20	66,924.00

REIMBURSEMENT:

* JCODE FOR MEDICARE IS J0349O
* MEDICAID REIMBURSEMENT IS AUTOMATIC
* ACCESS TO CARE PROGRAM FOR INDIGENT PATIENTS
  PHONE # FOR HOSPITALS IS 800-866-6273
  PHONE # FOR M.D.'S IS 800-729-4544

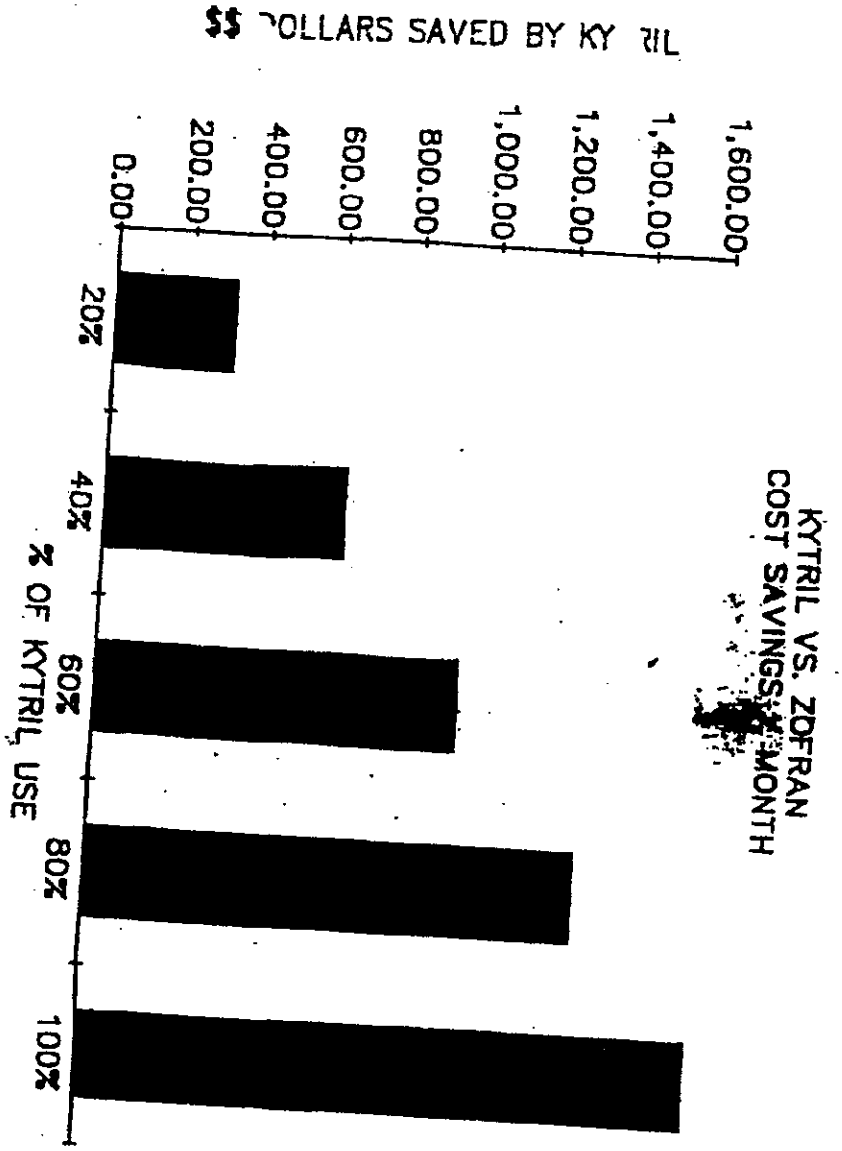
TIPS TO EXPEDITE MEDICARE AND MEDICAID CLAIMS:

* MEDICARE-USE ABOVE TEMPORARY JCODE AND WRITE ON THE FORM "KYTRIL RECENTLY APPROVED BY FDA" (SHOULD TAKE 35 DAYS TO GET REIMBURSEMENT)
* MEDICAID-PUT KYTRIL NDC # 0029-4149-01 ON CLAIM ... FOR QUESTIONS REGARDING MEDICARE AND MEDICAID, CALL 800-699-3806

ADVANTAGES:

KYTRIL REPRESENTS AN ADVANCEMENT IN THE TREATMENT OF CINV. IT REPRESENTS THE NEXT GENERATION OF 5HT3 AGONISTS

* EXTENDED HALF LIFE, MORE THAN DOUBLING THAT OF THE OTHER 5HT3
* TRUE 24 HOUR CONTROL
* EASE OF ADMINISTRATION (1 DOSE FOR EVERYONE, AND A 5 MINUTE INFUSION)
* STRINGENT EVALUATION CRITERIA (NO DEX., NO VOMITS ALLOWED) TO ESTABLISH EFFICACY.
* BENIGN SAFETY PROFILE.



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GSK- MDL- KYO4
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SB
SmithKline Beecham

Via Facsimile
and First Class Mail

February 7, 1995

Marianna Carter
Associate General Counsel
Glaxo Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Re: Promotional Complaint

Dear Ms. Carter:

This will confirm our telephone conversation of this morning regarding Tim Proctor's recent letter. In order for SB to perform any meaningful investigation of the claims made in that letter, we are in need of additional information. Specifically, in reference to the "homemade" materials that you reference as attachments "P" through "N" and "Q", we are interested in receiving information regarding (i) the location where these materials were allegedly left; (ii) the name of the physician or other healthcare professional to whom they were allegedly delivered; (iii) the date on which they were either delivered or retrieved; and (iv) the name of the SB representative, if known.

Use of "homemade" promotional materials is against SB policy. As I am sure that you can appreciate, if these materials are being generated by SB sales consultants, we are interesting in identifying them and taking appropriate disciplinary action. To that end, I will look forward to receiving any additional information that you may be able to provide.

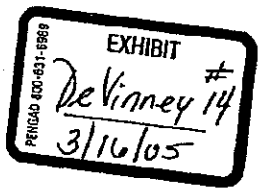
Very truly yours,

Ursula B. Bartels
Vice President and
Associate General Counsel

One Franklin Plaza, PO Box 7929, Philadelphia, PA 19101. Telephone (215) 751 4000 Fax (215) 751 3400.

bcc:

George Abercrombie	A3421
Tim Arendt	F1191
Chuck Bramlage	F1170
Clint Burrus	A3416
David Cory	F1190
Jim Daly	A3424
Mike duToit	A2136
Chris Foy	A3442
Mark Glackin	F1218
Jackie Hall	A3555
Doug Helling	F1198
Stan Hull	B2118
Gary Kirby	A3438
Ken Lowry	CN216
Ken Marshall	F1193
Lu McLeod	A3408
Allison Micich	F1217
Gil Mott	A3446
Rick Painter	F1199
Mike Pucci	D308
Fred Schmid	F1196
Steve Skolsky	F1169
Ron Stanton	A3450
Steve Stefano	A3404
Patty Tootle	F1195
Tim Tyson	A3454



SmithKline Beecham

Ursula B. Bartels
Vice President and Associate General Counsel

SENT VIA EXPRESS MAIL

February 22, 1995

Timothy D. Proctor
Senior Vice President, General Counsel and Secretary
Glaxo Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Dear Tim:

This is in response to your letter to Charles Wakerley dated February 6, 1994 regarding Kytril promotion. First, permit me to say that we appreciate your bringing these matters to our attention. We are in agreement that self-policing on these matters is in the best interest of the industry. To that end, in addition to responding to your letter, I have taken this opportunity to alert you to some ongoing concerns of SB relating to Zofran promotion, including: a homemade cost comparison piece that is very similar to the ones to which you have objected; a Fraud & Abuse concern regarding non-hospital reimbursement; and a promotional concern relating to several symposia sponsored by your subsidiary, Cerenex.

You letter was divided into four issues, which I will address in the order in which you raised them.

1. Alleged Promotion of Unapproved Kytril Doses

Your letter states that our promotional pieces contain data relating a 40 mcg./kg dose of Kytril. This was of concern to you since the approved dose of Kytril is 10 mcg./kg. As you may know, most of the clinical studies performed with Kytril were done with the 40 mcg dose. Dose ranging studies showed the doses of 10 mcg/kg and 40 mcg/kg to have comparable efficacy, and 10 mcg/kg was ultimately selected as the appropriate dosage. FDA has permitted us to use the 40 mcg data with appropriate statements, including the statement that "There was no statistically significant difference between the effect of these doses. Therefore the 10 mcg/kg was selected

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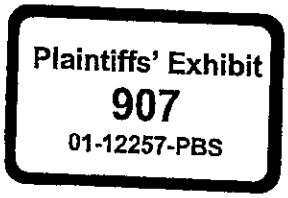

as the recommended dose." All FDA guidelines regarding the use of the 40 mcg. data were observed in the production of the pieces that you referenced in your letter. Indeed, two of the pieces, the launch sales aid and Slim Jim KY1014, were pre-cleared with DDMAC at the time of the launch.

2. "Homemade" Cost Comparisons

My concern over these "homemade" pieces, particularly the Fraud & Abuse considerations that you point out, prompted me to call you on the date that I received your letter. At your suggestion, I spoke to Glaxo Associate General Counsel Adrianna Carter, and requested that she facilitate our further investigation of these materials by providing us with any further details Glaxo might have regarding where the pieces were found, who created them, etc. I have confirmed this request to Ms. Carter in writing. Any help that you could provide would be most appreciated.

Without more information, we are unable to confirm that any of these materials were generated by our sales consultants. We are further unable to explore what was intended by the content of these materials in respect of reimbursement issues. Nothwithstanding these qualifications, our concern over the possibility of such potential violations prompted us to issue a phonemail broadcast reminder to all SB sales consultants. On February 7, 1995, SB Vice President of Sales, Walter Graham, strongly reminded all SB consultants that the use of "homemade" promotional materials and/or any encouragement of improper billing practices by physicians are serious breaches of SB policy and could subject the violator to discipline, up to and including termination of employment. The phonemail was followed-up by a memo to sales management.

Regarding similar concerns, we would like to draw your attention to reports we are receiving from our field force regarding reimbursement issues. In an apparent effort to increase reimbursement to physicians and clinics, effective 1/10/95, Glaxo increased AWP for Zofran by 8.5%, while simultaneously fully discounting this increase to physicians. The latter was accomplished by a 14% rebate available to wholesalers on all non-hospital Zofran sales of the multi-dose vial. The net effect of these adjustments is to increase the amount of reimbursement available to physicians from Medicare and other third party payors whose reimbursement is based on AWP. Since the net price paid to Glaxo for the non-hospital sales of the Zofran multi-dose vial is actually lower, it does not appear that the increase in AWP was designed to increase revenue per unit to Glaxo. Absent any other tenable explanation, this adjustment appears to reflect an intent to induce physicians to purchase Zofran based on the opportunity to receive increased reimbursement from Medicare and other third party payors. In fact, we have had numerous verbal reports from the field concerning Glaxo representatives who

are now selling Zofran based on the opportunity for physicians to receive a higher reimbursement from Medicare and other third-party payors while the cost to the physician of Zofran has not changed.

Attachment 1 is an example of the kind of "homemade" cost comparisons that were being disseminated in the field by Glaxo representatives prior to the recent change in AWP. The piece contains two overt factual inaccuracies that are misleading to the reader. First, Kytril is an infusion, not an IV push as suggested in the piece. Second, the Kytril "J" code went into effect January 1, 1995. We will provide you with any more recent examples that are picked up in the field. To the extent that details are available regarding any such materials, we will be happy to provide them to you in order to facilitate your investigation.

3. Promotion in Symposia and Conferences

Under this heading you reference slides from a presentation made by Dr. Carl Friedman nearly a year ago (March 10, 1994) in Puerto Rico. With respect to your concern regarding the use of 40 mcg. data in this presentation, please refer to the information set forth above in paragraph 1.

Dr. Friedman's objective in this presentation was to give oncologists a basic understanding of SB's clinical trials with Kytril Injection. To that end, the slides referenced SB's clinical trials of Kytril versus chlorpromazine/dexamethasone. As you may be aware, these trials are included in the Kytril labeling. Additionally, the slides from this talk received the benefit of review and comment by DDMAC in connection with a separate presentation by another presenter. The one item included in Dr. Friedman's talk that was absent from the materials that received FDA review was the slide on Kytril versus metoclopramide/dexamethasone. As part of this investigation of the concerns raised by your letter, we have drawn this slide to the attention of Dr. Friedman and our Kytril Product team. To the extent that it contains information that is not part of the permitted labeling, it will not be used for promotional purposes.

The unreferenced pricing information which you included as part of Exhibit "O" was not part of Dr. Friedman's presentation. We are treating that piece as part of the materials addressed in point 2, above.

The second program to which you objected under this heading is a symposium entitled "Chemotherapy Induced Nausea and Vomiting - Past and Present". This CE accredited program was presented by the Oncology Nurses Association ("ONA") in association with Scientific Therapeutics Information, Inc. ("STI") in connection with the Oncology Nursing Society's 19th Annual Congress on May 5, 1994.

bcc:
Walt Graham
Bill DeVinney
Howard Pien
Jerry Karabelas
Colleen Bennett
Carl Friedman
Olivia Pinkett
Bob Powell
Dick Van Thiel

SmithKline Beecham

Ursula B. Bartels
Vice President and Associate General Counsel

SENT VIA EXPRESS MAIL

February

Timothy D. Proctor
Senior Vice President, General Counsel and Secretary
Glaxo Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Dear Tim:

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Contrary to the suggestion made in your letter, our investigation has disclosed that this symposium was conducted pursuant to a Grant Agreement that conforms in all respects to FDA's Draft Policy on Industry Supported Scientific and Educational Activities ("Draft Policy"). Consistent with that Draft Policy, ONA/STI had complete control over the content of the program, and the agreements specifically recite that "[t]he program will be independent of SB's influence".

Finally, we note that Glaxo's Cerenex Pharmaceuticals division sponsored no fewer than four symposia at the same conference. (See Attachment 2). In fact, three of the four symposia appear to be repeat performances of the same presentation, held from 6:00 to 8:00 on the three successive mornings of the conference. As you know, FDA's Draft Policy notes that repeated performances are a primary factor to be considered in determining the "independence" of a particular program. In fact, the Draft Policy states that "If multiple performances of the same program are held, the agency may exercise a higher level of scrutiny compared with single programs." (57 FR 56412, 56413 (November 27, 1992)).

4. Promotion of Unapproved Tablet Form of Kytril

Your letter states that a journal article on the topic of Kytril oral was "delivered to a healthcare professional by an SKB representative last month". As noted above, I requested that Ms. Carter send me any additional information that she can find regarding this alleged incident. Upon receipt of such information, we will investigate the matter further and take whatever actions are warranted. Consistent with federal law and regulations, it is against SB policy for employees to commercialize unapproved products or indications.

I hope that you find this letter to be responsive to your concerns. To the extent that you are able to provide us with any additional details, we will continue our investigation and provide you with a further reply if warranted. Regarding the issues raised in connection with Glaxo promotion, we would appreciate your assurances that appropriate investigation and follow-up will occur.

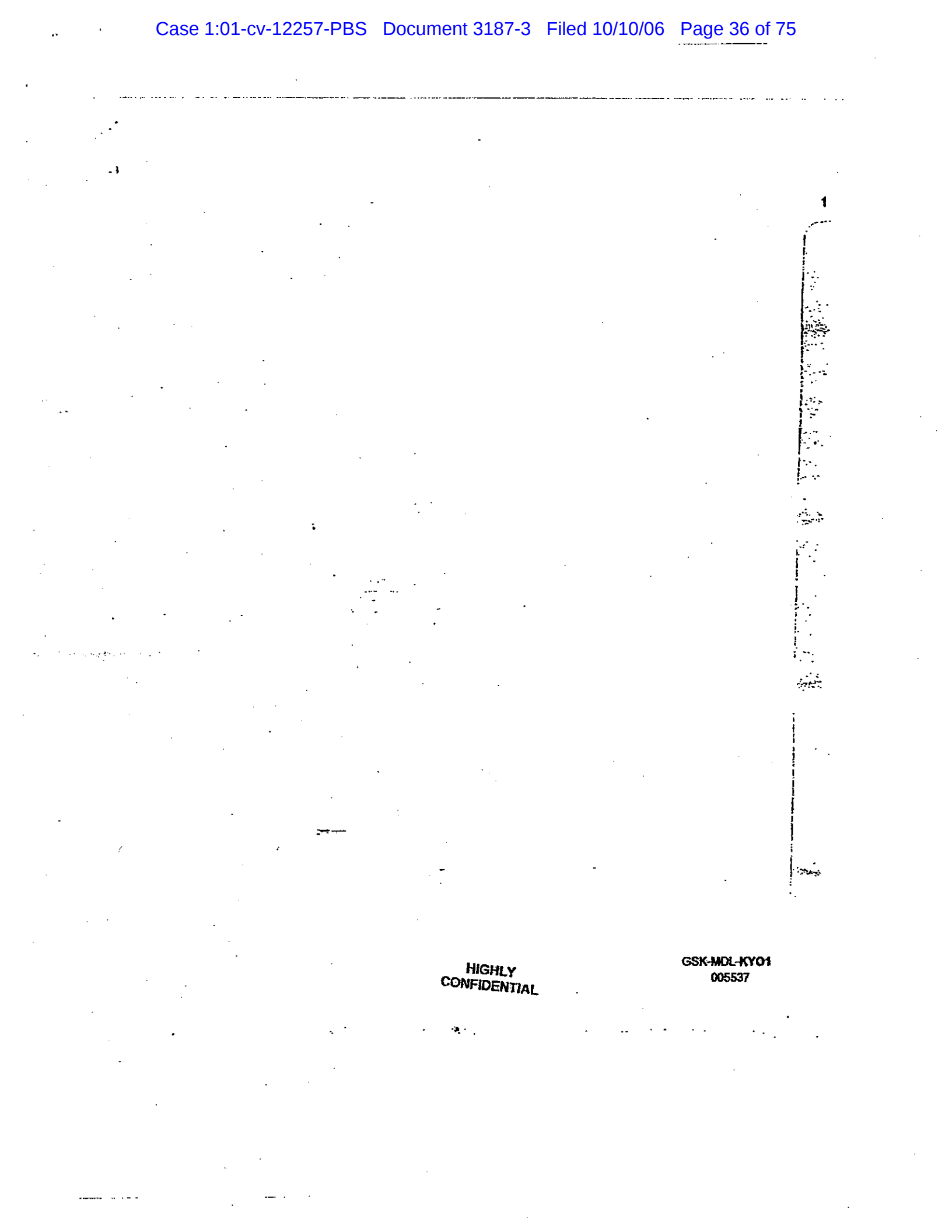
Very truly yours,

Ursula B. Bartels

cc: Charles Wakerley

Enclosure

bcc:
Walt Graham
Bill DeVinney
Howard Pien
Jerry Karabelas
Colleen Bennett
Carl Friedman
Olivia Pinkett
Bob Powell
Dick Van Thiel



Attachment 1

ZOFRAN AWP=$214/40MG=$5.35/MG
$171.20/32MG 80%(AWP)=$136.96

KYTRIL AWP $166/ML
$132.80/10McGM

ZOFRAN CONTRACT $172/40MG=$4.30MG
$137.60/32MG

ZOFRAN 32MG=$137.60
KYTRIL 10McGM=$132.80 DIFF $4.80

REIMB: ZF-CHEMO INFUSION 1HR (CODE 96410)
$44.95 X 80%=$35.96
KYTRIL IV PUSH $25.90 X 80%=$20.72
DIFF REIMB $15.24

Z-CODE ZOFRAN J-2405
KYTRIL CANNOT APPLY FOR J CODE TILL APRIL 1995 WILL BE JAN 1996 TO RECEIVE CODE

ZOFRAN MDV* CONTAINS PRESERVATIVES* CAN USE LEFTOVER MEDICATION AFTER 24HRS* ELIMINATES ANY WASTE*
KYTRIL SDV* MUST DISCARD AFTER OPENED IN 23HRS*

MEDICARE FEE SCHEDULE RESTRICTIONS: MEMO AUG 1992 SEPARATE PAYMENTS MAY BE MADE FOR EACH CHEMO AGENT FURNISHED ON DAY OF CHEMOTHERAPY ADMINISTERED USING HCPCS CODES TO BILL FOR DRUGS USED. IF,HOWEVER, MULTIPLE DRUGS ARE FURNISHED SEPARATELY, ONLY A SINGLE CHEMO THERAPY ADMINISTRATION CODE SHOULD BE USED. THEREFORE, IF MULTIPLE DRUGS ARE ADMINISTERED BY "PUSH" TECHNIQUE, ONLY ONE ADMINISTRATION CODE WILL BE RECOGNIZED. SIMILARLY, IN CASES WHERE CHEMOTHERAPY ADMINISTRATION FOR ONE DRUG IS BY INFUSION AND FOR ANOTHER DRUG BY PUSH, ONLY THE INFUSION CODE WILL BE REIMBURSED.
* reimbursement greater for infusion

Attachment 2

ONCOLOGY NURSING SOCIETY 19TH ANNUAL CONGRESS
MAY 4-7, 1994/CINCINNATI, OHIO

ANCILLARY EDUCATIONAL PROGRAMS SCHEDULE

DATE	TIME	EDUCATIONAL PROGRAM/SPONSOR
WEDNESDAY, MAY 4	6:00 AM - 8:00 AM	SYMPOSIA Sponsored by CERENEX PHARMACEUTICALS
	6:00 AM - 8:00 AM	EMPOWERING THE NURSE: APPLYING NEW FINDINGS TO CLINICAL PRACTICE Sponsored by AMGEN
	6:30 AM - 8:30 AM	COMMUNICATING ABOUT NSCLC: THE NURSING ROLE IN HELPING PATIENTS UNDERSTAND SPONSORED BY BURROUGHS WELLCOME CO.
	6:30 AM - 9:00 AM	SYMPOSIA Sponsored by ROCHE
	1:00 PM - 3:00 PM	SYMPOSIA Sponsored by ROCHE
	7:00 PM - 10:00 PM	THE AHCPR CHRONIC CANCER PAIN MANAGEMENT GUIDELINES: MOVING FROM THE BOOKSHELF INTO PRACTICE Sponsored by THE PURDUE FREDERICK COMPANY

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DAU248 (2/3/94)

ONCOLOGY NURSING SOCIETY 19TH ANNUAL CONGRESS
MAY 4-7, 1994/CINCINNATI, OHIO

ANCILLARY EDUCATIONAL PROGRAMS SCHEDULE

DATE	TIME	EDUCATIONAL PROGRAM/SPONSOR
THURSDAY, MAY 5	6:00 AM - 8:00 AM	SYMPOSIA Sponsored by CERENEX PHARMACEUTICALS
	6:00 AM - 8:30 AM	FIGHTING FATIGUE: NURSING ISSUES IN CANCER MANAGEMENT Sponsored by ORTHO BIOTECH, INC.
	6:00 AM - 8:30 AM	BREAST CANCER REHABILITATION: EXPLORING THE ROLE OF THE MASTECTOMY NURSE PROSTHETIST Sponsored by COLOPLAST
	6:00 AM - 8:30 AM	COMMUNICATING ABOUT NSCLC: THE NURSING ROLE IN HELPING PATIENTS UNDERSTAND Sponsored by BURROUGHS WELLCOME CO.
	7:00 AM - 8:30 AM	MULTI CHANNEL TECHNOLOGY IN THE BONE MARROW PATIENT Sponsored by ABBOTT, HOSPITAL PRODUCTS DIVISION
	1:00 PM - 3:00 PM	SYMPOSIA Sponsored by JANSSEN PHARMACEUTICA
	1:15 PM - 2:45 PM	UNIT BASED NURSING RESEARCH Sponsored by NATIONAL INSTITUTE OF HEALTH. CLINICAL CENTER NURSING DEPARTMENT
	5:00 PM - 9:00 PM	CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING: PAST AND PRESENT Sponsored by SMITH KLINE BEECHAM PHARMACEUTICALS
	5:45 PM - 10:00 PM	KEEPING PACE WITH PAIN MANAGEMENT Sponsored by KNOLL PHARMACEUTICAL COMPANY
	6:30 PM - 9:00 PM	COMMUNICATING ABOUT NSCLC: THE NURSING ROLE IN HELPING PATIENTS UNDERSTAND SPONSORED BY BURROUGHS WELLCOME CO.

ONCOLOGY NURSING SOCIETY 19TH ANNUAL CONGRESS
MAY 4-7, 1994/CINCINNATI, OHIO

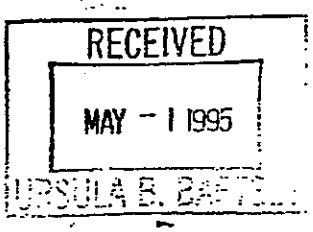
ANCILLARY EDUCATIONAL PROGRAMS SCHEDULE

DATE	TIME	EDUCATIONAL PROGRAM/SPONSOR
FRIDAY, MAY 6	8:00 AM - 8:00 AM	SYMPOSIA Sponsored by CERENEX PHARMACEUTICALS
	6:00 AM - 8:30 AM	COMMUNICATING ABOUT NSCLC: THE NURSING ROLE IN HELPING PATIENTS UNDERSTAND Sponsored by BURROUGHS WELLCOME CO.
	6:00 AM - 8:30 AM	BREAST CANCER REHABILITATION: EXPLORING THE ROLE OF THE MASTECTOMY NURSE PROSTHETIST Sponsored by COLOPLAST
	6:00 AM - 8:30 AM	ORAL SYMPTOMS MANAGEMENT FOR IMPROVING PATIENT QUALITY OF LIFE Sponsored by UNIMED, INC.
	6:30 AM - 8:30 AM	PATIENT DIRECTIVES IN CANCER CARE: ETHICS AND DECISION-MAKING Sponsored by WYETH-AYERST LABORATORIES
	7:00 AM - 8:30 AM	ONCC BREAKFAST Sponsored by WYETH-AYERST LABORATORIES
	1:00 PM - 3:00 PM	PRIVATE PRACTICE NURSING Sponsored by PHARMACIA ADRIA
	1:15 PM - 2:45 PM	COMFORTING CHILDREN DURING RADIO-THERAPY Sponsored by SCHERING
	6:30 PM - 9:00 PM	COMMUNICATING ABOUT NSCLC: THE NURSING ROLE IN HELPING PATIENTS UNDERSTAND Sponsored by BURROUGHS WELLCOME CO.
SATURDAY, MAY 7	5:00 PM - 9:00 PM	QUALITY OF LIFE ISSUES DURING THE ACUTE AND LONG-TERM SURVIVORSHIP PERIOD: PATIENT STORIES Sponsored by CERENEX PHARMACEUTICALS, DIVISION OF OLAXO, INC.

Glaxo

Adrianna L. Carter
Assistant General Counsel

April 25, 1995



Ursula B. Bartels, Esq.
Vice President and Associate
General Counsel
SmithKline Beecham
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

Dear Ms. Bartels:

This is in response to your February 22 letter to Timothy Proctor which was in response to a letter from Mr. Proctor dated February 6, 1995. We appreciate your prompt response and the actions you have taken to address some of the issues identified in Mr. Proctor's letter. However, it is clear from your letter, and we would agree, that several key issues remain unresolved. These issues are addressed below.

1. Promotion of Unapproved Kytril™ (granisetron HCL) Doses

Your response to our objection to the use of unapproved doses and the omission of fair balance in Kytril promotional pieces was that the FDA had essentially reviewed and approved the data presentations used to promote Kytril. This raises the issue of fairness for Glaxo since the FDA has recently objected to the distribution of dose ranging studies for Zofran® (ondansetron hcl) on the grounds that the studies contain unapproved doses. In addition, the FDA has apparently imposed upon Glaxo a more stringent standard for fair balance in promotional pieces. Given this, we will pursue these issues directly with DDMAC from the standpoint that the restrictions imposed on Zofran in these areas should be no more restrictive than those applicable to Kytril.

2. Distribution of "Homemade" Cost Comparisons

Attachment A is being provided in response to your request for additional information regarding the examples included in the February 6 letter of improper homemade cost

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comparisons distributed to health care professionals by SKB representatives. This attachment includes, where this information was available, the names of the cities where the homemade pieces (which were included as attachments to Mr. Proctor's February 6 letter) were discovered. In a few cases, we were able to identify and have provided to you the name of the SKB representative who left the materials. I have also included as Exhibit A1 a recent example of the type of homemade materials described in the February 6 letter. As you can see, this one includes the business card of the SKB representative who distributed the piece. This piece contains a price comparison that does not meet the standards set out by FDA. In addition, false and misleading statements are made about Zofran, including a statement that retreatment with tablets is required when Zofran is administered. Exhibit A2 is another example of an inappropriate price comparison. The comparison, along with a copy of a letter from M. D. Anderson Cancer Center and the antimetic guidelines for Sloan Kettering, were left by Stan Wallace of Decatur, Alabama with the Tennessee Valley Blood and Cancer Center. Exhibit A3 is another recent example left by an SKB representative in the Tidewater, Virginia area. Exhibit A4 which provides out of label stability information on Kytril was left recently by An SKB representative named Jack W. Griffith.

Your letter of February 22 included a homemade piece allegedly left with a healthcare professional by a Cerenex representative. As stated in your letter, it is difficult if not impossible to investigate these cases when no information as to the place and parties involved is provided. Therefore, we are requesting that any available information, including the place and date when the material was left, along with the and name of the individual who allegedly left the piece, be provided to us. Glaxo has a strict policy prohibiting the use and/or distribution of homemade materials. Our representatives have been recently reminded of this policy by voice mail and through a written communication which required a written acknowledgment of their receipt and understanding of this policy. For this reason, we are particularly interested in the date this sheet was allegedly distributed.

3. Fraud and Abuse Issues

Your letter of February 22 states your concern regarding reimbursement issues associated with its recent price increase for Zofran Injection. According to this letter, "this [price] adjustment appears to reflect an intent to induce physicians to purchase Zofran based on the opportunity to receive increased reimbursement to Medicare. . ." and Glaxo representatives "are now selling Zofran based on the opportunity for physicians to receive a higher reimbursement from Medicare and other third-party payers while the cost to the physician of Zofran has not changed." We do not agree with the implication that a routine, across the board price increase on a product represents illegal remuneration. It is true that, despite a price increase, some physicians and other healthcare professionals will not see the higher price as the result of rebates or other incentives. Any rebates or other incentives offered by Glaxo to

providers comply with the requirements of Section 1128(b) of the Social Security Act applicable discount "safe harbor" regulations in 42 C.F.R. §1001.952 (h). It is also true that our sales representatives have been explaining the relationship between the price and Medicare reimbursement for Zofran to physicians. However, unlike SKB personnel, Glaxo representatives are not promoting Zofran on the grounds that the Medicare "profit" is more favorable than those for competing products.

In addition, SKB representatives have been instructing physicians to use one vial of Kytril for two or three patients and file claims indicating that they had in fact used one separate vial for each patient. This is reflected in some of the homemade pieces included in Tim Proctor's February 6 letter. We, nevertheless, appreciate the actions described in your letter to put an end to these activities. Unfortunately, despite your efforts, these activities are still ongoing. As an example, I have included as Exhibit A5 a copy of a homemade piece which was left by an SKB representative named M. J. Bartolomeo at a doctor's office in Michigan. The piece presents (incorrect) "profit" comparisons between Zofran and Kytril and also incorrectly indicates that Kytril is reimbursed at 100% while Zofran is reimbursed at the 80% level. The piece also recommends unapproved dosage levels for Kytril. Exhibit A6 includes examples of materials being left with physicians containing false and misleading comparisons between granisetron and Zofran.

4. Promotion in Symposia and Conferences

The letter of February 7 also objected to a symposium entitled "Chemotherapy Induced Nausea and Vomiting-Past and Present." This symposium presented unapproved objectionable claims for Kytril, including comparative comparisons between Kytril and Zofran. Your response was that the symposium "conforms in all respects to the FDA's Draft Policy on Industry Supported Scientific and Educational Activities ('Draft Policy')." That policy states that the agency will not attempt to regulate programs that are educational and nonpromotional in nature. The Draft Policy also expresses a strong willingness to examine all relevant facts including the existence of a written agreement to determine if, in fact, a program is independent. Areas of inquiry would include the level of involvement of the supporting company of the program content and objectivity and balance "when a product marketed by the company or in competition with such product is to be the subject of substantial discussion."

The presentation given by Lorraine Baltzer Cleri as part of this symposium would not meet the standards set out by the FDA. Ms. Cleri's presentation was clearly a promotional discussion of Kytril. The introduction to the presentation includes statements such as, "Studies in the ferret have also shown that the duration of effect of granisetron is twice that see with ondansetron." and "In this study, more patients preferred granisetron over the other two agents (P<.001)." The introduction and the slides also include extensive materials regarding a comparison of higher than approved

doses of Kytril with lower than approved doses of Zofran. It is also obvious that some of Ms. Cleri's slides had been prepared by SKB. At least one of them can be found in the SKB-generated presentation of Dr. Friedman which was included in the February 6 letter to Mr. Wakerley as Exhibit "O". Given this, our position remains that SKB is improperly using company-sponsored symposia to disseminate inappropriate and misleading information on Zofran and Kytril. More recently, SKB representatives in the Cincinnati and Dayton, Ohio areas have used meetings, which included dinner and a Broadway show, to compare an out of label dose of Zofran (8 mg) with an out of label dose of Kytril (3 mg). The Pharm D making this presentation also included in the presentation a cost comparison between Zofran and Kytril. I have also included as Exhibit B a copy of a booklet entitled "Symposium Highlights Bulletin" which was mailed out to members of ASHP. The Bulletin contains highlights of a December 7, 1994 SKB sponsored ASHP symposium entitled "Therapeutic Consideration for Antiemetic Therapy in Oncology Patients." Like the symposium described above, this presentation appears to be nothing more than a promotional program for Kytril. Invalid or out of label information was presented on Kytril and Zofran. The summary ends with a discussion which purports to prove that granisetron is more cost effective than ondansetron. This is another example of a program that does not meet the FDA standards for independent programs.

Your February 22 letter indicates that you may have some concerns about the Glaxo symposia held during the same meeting as the one described above. Attached as Exhibit B1 is a copy of the pamphlet which described these symposia. These three symposia, entitled "The Cancer Experience in the Family," "Aggressive Cancer Treatment: Spotlight on Quality of Life," and "Nausea and Vomiting: Combining Holistic Care with Scientific Knowledge," met all the standards for independence and did not serve as vehicles to make promotional presentations on Zofran.

5. Promotion of Kytril Tablets

Finally, your letter of February 22 requested additional information on the preapproval promotion of Kytril Tablets. The reprint entitled: Oral granisetron alone and in combination with dexamethasone: "A double-blind randomized comparison against high dose metoclopramide plus dexamethasone in prevention of cisplatin-induced emesis" which was included as Exhibit O of the February 6 letter was most recently left with an account in early February by Glenda Lewis, a SKB representative. I have also attached as Exhibit C a copy of a flyer handed out by an SKB representative named Phil Ra. As you can see, the flyer is an invitation to a presentation on Kytril Tablets. The Cincinnati/Dayton, Ohio meetings described above have also included a preapproval discussion on the use of Kytril Tablets.

As stated previously, we do appreciate the response we have gotten to date to our concerns. I look forward to resolving the remaining issues in a similar, expeditious manner.

Very truly yours,

Adrianna L. Carter

ALC/mj

Attachments

Attachment	Area	SKB Rep
D	Miami, VA	
E	Ocean County, NJ	
F	Denville, NJ	Heidi Haas
G	Escondido, CA	
H	Nashville, TN	
I	_____	
J	Brunswick, GA	
K	Taunton, MA	
L	Denville, NJ	Heidi Haas
M	Darien, IL	
N	Portland, OR (Kytril v. Zofran cost sheet) Philadelphia, PA ("Monthly Cost Savings") Midland, TX (Cost Calculator Sheet-Kytril) Ocean County, NJ	

EXHIBIT A1

SB
SmithKline Beecham
Pharmaceuticals

Jim Dymski
Senior Pharmaceutical Consultant
Hospital Product Specialist

427 Hogestown Road, Mechanicsburg, PA 17055
Telephone (717) 691 1196. Regional Office (609) 596 5338.

1/16/95

Diane,

Here is the information we spoke about on the phone last week. I have continued to try to get in contact w/ Rich in Pharmacy with no luck @ all.

I hope a direct request from Dr Carter to have Lytril available for use in both office and hospital will be the step to have Lytril available for your evaluation

Price information is as follows
$173.00 for Zofran 40mg multi use vial
$132.00 for Lytril

* Various cost comparison for different pts

32mg Zofran = $137.20 per patient
.7mg of Lytril = 92.40 per patient
70kg pt 10mg/kg $44.80 per patient savings

24mg Zofran = $104.40 per patient
.7mg of Lytril = 92.40 per patient
70kg pt 8mg/kg $12.00 per patient savings

ORDER No. 833-3

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000200

Dosing of Kytril is based on patient weight 10 ung/kg.

Cost savings not noticed right up front is the lack of readministering. Kytril doesn't need to be readministered. Zofran may need oral tablet follow up. Kytril has the advantage of much longer half life.

Jim

P.S. See you Thurs @ CP06.

ORDER No. 033-3

HIGHLY CONFIDENTIAL

EXHIBIT A2

$16,796.00

PROCRIT
EPOETIN ALFA

Available in 2000, 3000, 4000, and 10,000 U/mL single-use vials.
Supplied in packages of six.

KYTRIL = 1 mg vial per patient
$115.00 = per vial cost
$166.00 - Medicare allowance
$ 51.00 - profit

ZOFRAN - 32 mg per patient
$ 128.00 = cost for 32 mg
166.08 - medicare allowance
$ 38.08 - profit

$ 51.00 - profit from Kytril
$ 38.02 - profit from Zofran
$ 12.92 more per Kytril pt

$ 12.92
x 25 - medicare patients per wk
$323.00 - per week
x 52.00 - weeks per year
$16,796

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GSK-MDL-KY03
000202

THE UNIVERSITY OF TEXAS
M.D. ANDERSON CANCER CENTER

Division of Pharmacy-40

April 13, 1994

MEMORANDUM

TO: Michael J. Keating, M.D.
Chairman, Pharmacy and Therapeutics Committee

FROM: Roger W. Anderson
Head, Division of Pharmacy

SUBJ: Formulary Status of Granisetron (Kytril®) Injection

Following the preliminary review of granisetron injection at the March 2, 1994 Pharmacy and Therapeutics Committee meeting, we have conducted an extensive analysis of this agent. Emphasis of this review has been on the potential therapeutic and fiscal impact of this anti-emetic agent for our patients and the institution. The initial Pharmacy and Therapeutics Committee recommendation was to take no formulary action until specific pricing information is available and until efforts toward comparative ondansetron-granisetron clinical trials are pursued. A protocol for a comparative ondansetron-granisetron clinical trial (co-sponsored by Glaxo and Smith Kline-Beecham, including free drug) will be submitted to the Surveillance Committee in April. In addition, a price quote was given to us on April 12, 1994. Conversion of current IV ondansetron doses of 30mg/day to granisetron 1mg IV (fixed dose) would result in an annual cost savings of approximately 1.5 million dollars. Discussions with personnel at Memorial Sloan-Kettering reveal that preliminary use (approximately 40 patients) of granisetron 1mg IV with dexamethasone 20mg has been as effective as ondansetron 30mg plus dexamethasone. Also, no additional daily granisetron doses have been required.

Based on the economic impact of this solid price quote for granisetron, and on preliminary clinical findings, I feel that we should pursue the immediate addition of granisetron to the formulary and to closely monitor and document the efficacy of this agent.

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Sloan Kettering

MSKCC ANTIEMETIC GUIDELINES

Adult

ACUTE EMESIS REGIMEN:

Dexamethasone Plus a Serotonin Antagonist
All adult patients receiving granisetron or ondansetron should be treated concomitandy with DEXAMETHASONE. An exception exists for Leukemia, Lymphoma, Multiple Myeloma and Bone Marrow Transplant Patients for whom specific protocols should be referred to.

DEXAMETHASONE — 20 mg IV x 1 given 15 minutes prior to chemotherapy. Administer over 15 minutes.

Highly Emetogenic:

GRANISETRON — 10 mcg/kg IVPB 30 minutes before chemotherapy x 1 dose. Administer over 5 minutes

Moderately Emetogenic:

GRANISETRON — 10 mcg/kg IVPB 30 minutes before chemotherapy x 1 dose. Administer over 5 minutes.

Mildly Emetogenic:

ONDANSETRON — 8 mg IVPB 30 minutes before chemotherapy x 1 dose. Administer over 15 minutes.

Continuous Infusion:

ONDANSETRON — 8 mg IVPB given 30 minutes prior to chemotherapy on Day 1 only. Administer over 15 minutes. Follow immediately with:

ONDANSETRON — 25 mg/250 cc D_5W to infuse at 10 cc/hour (Rate 1 mg/hour) for 24 hours x _____ days.

BREAKTHROUGH EMESIS REGIMEN:

If a patient requests additional antiemetics or vomits ≥ 3 times, give:

Metoclopramide — (2 mg/kg)____mg IVPB x 1 dose then q 3 - 4 hours, PRN ONLY for nausea and vomiting.

Diphenhydramine — 50 mg IV every 30 minutes PRN ONLY for restless or acute dystonic reactions.

DELAYED EMESIS REGIMEN:

To begin at 6 am the day following chemotherapy:

Metoclopramide — (0.5 mg/kg) ____ mg IV QID x 1 day (Day 1), then
(0.5 mg/kg) ____ mg IV/PO QID x 1 day (Day 2).

Dexamethasone — 8 mg IV BID x 1 day (Day 1), then
8 mg PO/IV BID x 1 day (Day 2), then
4 mg PO/IV BID x 2 days (Days 3 & 4)

Diphenhydramine — 50 mg PO every 4 hours PRN for restlessness or acute dystonic reactions

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Pediatrics

GRANISETRON — 10 mcg/kg IVPB 30 minutes before chemotherapy x 1 dose. Administer over 5 minutes.

EXHIBIT A3

SmithKline Beecham
Pharmaceuticals

ANTI-EMETIC COST ANALYSIS

PRODUCT	COST/VIAL	AVG/DOSE	COST/DOSE	%
KYTRIL (GRANISETRON) 1MG/1ML VIAL	$111.95	0.7MG	$78.37	36%
ZOFRAN (ONDANSETRON) 2MG/20ML VIAL	~~$161.00~~ 3/1 ↑ 172.92	32MG	~~$128.80~~ 137.33	-

TOTAL VIALS PURCHASED	ZOFRAN $	KYTRIL $	SAVINGS WITH KYTRIL
450	$72,450	$50,400	$22,050
500	80,500	56,000	24,500
550	88,550	61,600	26,950
600	96,660	67,200	29,400
650	104,650	72,800	31,850
700	112,700	78,400	34,300
750	120,750	84,000	36,750
800	123,300	89,600	39,200

*DRUG COSTS FROM FLORIDA INFUSION ON JANUARY 31, 1995.

*AVERAGE DOSE COMPARISON BASED ON A 70 KG PATIENT.

*ZOFRAN PRICE DOES NOT INCLUDE A 8.5% INCREASE STARTING ON FEBRUARY 1, 1995.

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GSK-MDL-KY03 000205

One Franklin Plaza, PO Box 7929, Philadelphia, PA 19101 Telephone (215) 751 4000 Fax (215) 751 3400

SmithKline Beecham Pharmaceuticals

EXHIBIT A4

[redacted]

Jack W. Griffith
Senior Key Physician Specialist

P.O. Box 749, Redlands, CA 92373
Regional Office (714) 588 1525.

ETODOLAC TABLETS 400mg

55 lbs 1/4

110 1/2

165 3/4

220 1 ml

Kytril

Room temp 3 days
Refrig 7 days
Frozen 30 days

WYETH-AYERST — A·H·ROBINS

[redacted]

HIGHLY CONFIDENTIAL

SmithKline Beecham
Pharmaceuticals

March 21, 1995

I am writing in response to your request for information regarding the efficacy and safety of *Kytril* (granisetron hydrochloride, SmithKline Beecham Pharmaceuticals) Tablets for the prevention of nausea and vomiting associated with emetogenic chemotherapy.

Overview of *Kytril* Tablets

Granisetron is a potent and highly selective antagonist of the serotonin-3 (5-HT_3) subtype of serotonin receptor and has negligible affinity for other receptors, including other subtypes of serotonin receptors and dopamine-2 receptors. In preclinical studies, granisetron produced an insurmountable blockade of vagus nerve 5-HT_3 receptors at serotonin concentrations of up to 100 micromolar.[1,2]

Kytril Tablets are indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin. The efficacy of oral *Kytril* in preventing nausea and vomiting associated with emetogenic chemotherapy has been documented in several small preliminary studies,[3-6] and in large randomized, double-blinded studies.[7-12] The recommended regimen for *Kytril* Tablets is two 1 mg tablets given on each day of chemotherapy administration.

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000207

One Franklin Plaza, PO Box 7929 Philadelphia, PA 19101 Telephone (215) 751 4000 Fax (215) 751 3400

The first tablet should be given up to 1 hour prior to chemotherapy and the second tablet should be given 12 hours after the first dose.[13] No dosage adjustment is recommended for elderly patients, or for patients with renal or hepatic impairment.

Kytril Tablets have been well tolerated in clinical trials. The most common adverse events noted during therapy with *Kytril* were constipation and headache. Other events reported include asthenia, abdominal pain, diarrhea and dizziness;[13] however, a causal relation of these events with *Kytril* Tablets is unclear.

Kytril is also available as an injectable product which is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin. The recommended regimen of *Kytril* Injection is a single 10 mcg/kg dose infused intravenously (IV) over 5 minutes, beginning within 30 minutes prior to the initiation of chemotherapy, and given only on the day(s) of chemotherapy.[14]

Dose-Ranging Studies

In a pilot study, 42 patients received one of the following oral *Kytril* regimens beginning 1 hour prior to the administration of chemotherapy: 0.25 mg x 1, 0.5 mg x 1, 1 mg twice daily x 2 doses or 2.5 mg twice daily x 2 doses.[3] Patients eligible for this study were chemotherapy naive and were to receive a cisplatin regimen ($\geq$ 50 mg/m^2). Seven of the 9 patients who received the 2.5 mg regimen were classified as complete responders at 24 hours; an identical rate of complete response was noted with the 1 mg regimen. In contrast, only 1 of 12 patients who received the 0.25 mg dose and 2 of 12 patients who received the 0.5 mg doses were classified as complete responders to oral *Kytril*.

In a subsequent double blind study, the efficacy of oral *Kytril* was examined in 930 chemotherapy-naive patients (at least 18 years of age) who were scheduled to receive moderately emetogenic chemotherapy.[7-9] The chemotherapeutic agents permitted were:

- carboplatin ($\geq$ 300 mg/m^2);
- cisplatin ($\geq$ 20 mg/m^2 and $\leq$ 50 mg/m^2);
- cyclophosphamide (oral $\geq$ 100 mg/m^2/day; intravenous $\geq$ 500 mg/m^2);
- dacarbazine ($\geq$ 350 mg/m^2 and $\leq$ 500 mg/m^2);
- doxorubicin ($\geq$ 40 mg/m^2 if used alone or $\geq$ 25 mg/m^2); and
- epirubicin ($\geq$ 75 mg/m^2 if used alone or $\geq$ 50 mg/m^2).

The patients were randomized to receive oral *Kytril* at a dose of 0.25 mg, 0.5 mg, 1 mg or 2 mg twice daily for 7 days.[7-9] The first dose of *Kytril* was administered 1 hour prior to the administration of chemotherapy and the subsequent doses were given at 12 hour intervals. The primary efficacy parameters were the proportion of patients who had a complete response (defined as no vomiting, no worse than mild nausea, received no additional antiemetics and not withdrawn from the study), the proportion of patients who had no vomiting and the proportion who had no nausea at 24 hours. In addition, the proportion of patients who had total control of nausea and vomiting (no vomiting, no nausea and no use of additional antiemetics) was also noted. The response rates are provided in Table 1.[7,9]

Table 1
Response at 24 Hours

	Dose of *Kytril*			
Efficacy parameter	0.25 mg bid (n=229)	0.5 mg bid (n=235)	1 mg bid (n=233)	2 mg bid (n=233)
Complete response	61%	70%*	81%*#	72%*
No vomiting	66%	77%*	88%*	79%*
No nausea	48%	57%	63%*	54%
Total control	45%	55%	60%*	52%

*$p < 0.01$, versus 0.25 mg bid
#$p < 0.01$, versus 0.5 mg bid

This study demonstrates that dosage regimens of 0.5 mg bid and greater were more effective than 0.25 mg bid; however, only the 1 mg bid regimen was superior to the 0.25 mg bid dosage on all efficacy parameters. The complete response rates were not altered significantly if the 121 patients who received oral cyclophosphamide as their primary chemotherapy agent are excluded from analysis.[7,9] Thus, the 1 mg bid dosage was the most effective regimen studied.

Efficacy in
Moderately Emetogenic Chemotherapy

The efficacy of oral *Kytril* in preventing nausea and vomiting associated with moderately emetogenic chemotherapy has been demonstrated in 3 double-blind studies, including the previously described dose-ranging study.[7,8,11,12]

In a second multicenter study, oral *Kytril* was compared with oral *Compazine* (prochlorperazine, SmithKline Beecham Pharmaceuticals) in 230 chemotherapy-naive patients (≥ 18 years of age) who were scheduled to receive moderately emetogenic chemotherapy.[7,11] These patients were randomized to receive either 1 mg bid of *Kytril* Tablets or 10 mg bid of *Compazine* Spansules for 7 days. The permitted chemotherapy agents were identical to those listed for the prior study, with the exception that oral cyclophosphamide and epirubicin were not allowed. The primary endpoints for efficacy were the proportion of patients who had total control of nausea and vomiting (as previously defined) and the proportion who had a complete response (as previously defined) at 24 hours. Secondary endpoints included the percentage of patients who had no emesis, no nausea or no use of additional antiemetics in the first 24 hours and the time to first nausea or vomiting. The results of this study are summarized in Table 2.

Table 2
Response to Oral *Kytril* or Oral *Compazine* at 24 Hours

	Study Group	
Efficacy parameter	Oral *Kytril* 1 mg bid (n=119)	Oral *Compazine* 10 mg bid (n=111)
Total control	58%*	33%
Complete response	74%*	41%
No vomiting	82%*	48%
No nausea	58%*	35%
No additional antiemetics	94%*	79%

*$p < 0.034$

As noted in Table 2, *Kytril* was more effective than *Compazine* in each of the efficacy parameters at 24 hours. In addition, the time to first emesis or first nausea was significantly delayed in the patients treated with *Kytril* Tablets compared to those treated with *Compazine* ($p < 0.02$). On day 2, significantly more *Kytril*- (82%) than *Compazine*-treated (68%) patients were free from emesis ($p = 0.016$); however, no significant differences were noted in the proportion of patients who were free from nausea (53% vs 49%, respectively). The proportion of patients who were free from emesis or nausea on the subsequent days (days 3-7) did not differ between the two groups. Yet, the rate of complete response at 7 days favored *Kytril* over *Compazine* (47% vs 32%, respectively, $p < 0.033$). Thus, *Kytril* at a dose of 1 mg bid was more effective than *Compazine* 10 mg bid in the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy.

In a third study, two regimens of oral *Kytril* were examined in 697 chemotherapy-naive patients who were scheduled to receive a moderately emetogenic chemotherapy regimen.[7,12] Beginning 1 hour prior to chemotherapy administration, the patients received either 1 mg bid or 2 mg once daily of oral *Kytril* in a randomized, double-blind fashion. Once again, the efficacy measures included the proportion of patients who experienced total control of nausea and vomiting (as defined previously), and the proportion who had no nausea, no vomiting or no use of rescue medications. The results are presented in Table 3.

Table 3
Response to Oral *Kytril* at 24 Hours

	Study Group	
Efficacy parameter	Oral *Kytril* 1 mg bid (n=354)	Oral *Kytril* 2 mg once daily (n=343)
Total control	51%	50%
No vomiting	82%	77%
No nausea	51%	53%
No additional antiemetics	80%	79%

No statistically significant differences were noted between the two treatment groups on any of the efficacy variables.

Efficacy in
Highly Emetogenic Chemotherapy

The efficacy of oral *Kytril* was examined in a double-blinded study of 357 chemotherapy naive patients who were scheduled to receive a cisplatin-based chemotherapy regimen (mean cisplatin dose for each group was approximately 80 mg/m^2).[7,10] Eligible patients were randomized to receive one of the following three antiemetic regimens:

a) oral *Kytril* 1 mg bid beginning 1 hour prior to the initiation of chemotherapy and continuing for a total of 7 days,

b) oral *Kytril* as described above plus a single 12 mg IV infusion of dexamethasone given 5 minutes prior to chemotherapy, or

c) intravenous metoclopramide (3 mg/kg just prior to chemotherapy followed by 4 mg/kg given as an 8 hour continuous infusion) plus a single dose of dexamethasone as described above; followed by an oral regimen of metoclopramide (10 mg tid) on days 1-6 (total regimen of 7 days).

Once again, the primary efficacy parameters (as previously defined) were the proportion of patients with total control of nausea and vomiting, complete response, no vomiting and no nausea at 24 hours. The results of this study are shown in Table 4.[7,10]

Table 4
Response Rates at 24 Hours

	Treatment Group		
Efficacy parameter	*Kytril* (n=119)	*Kytril* + dex (n=117)	Metoclopramide/dex (n=121)
Total control	44%	55%*	37%
Complete response	52%	65%#	52%
No vomiting	56%	66%	52%
No nausea	45%	57%	39%

*p = 0.007 vs metoclopramide + dexamethasone
#p = 0.044 vs *Kytril* & vs metoclopramide + dexamethasone

This study revealed no significant differences between the effectiveness of *Kytril* and intravenous metoclopramide plus dexamethasone in preventing acute nausea and vomiting. However, the addition of dexamethasone to oral *Kytril* significantly improved the rate of total control over metoclopramide plus dexamethasone, and the rate of complete response over *Kytril* alone and over metoclopramide/dexamethasone.[7,10]

Summary of Efficacy

Kytril, at an oral dose of 1 mg bid, is an effective antiemetic in patients who are receiving moderately emetogenic or highly emetogenic chemotherapy. Oral *Kytril* was more effective than oral *Compazine* (10 mg bid) and was as effective as high-dose intravenous metoclopramide plus dexamethasone in preventing chemotherapy-induced nausea and vomiting.

General Safety

Oral *Kytril* was administered to over 2600 patients in clinical trials and was generally well tolerated. Table 5 notes the most common adverse events ($\geq$ 5%) which occurred in patients treated with *Kytril* (1 mg bid for 1, 7 or 14 days) or with a comparator antiemetic regimen or with placebo.[13]

Table 5

Adverse event	Oral *Kytril* 1 mg bid (n=978)	Comparator* (n=599)	Placebo (n=185)
Headache	21%	13%	12%
Constipation	18%	16%	9%
Asthenia	14%	10%	4%
Diarrhea	8%	10%	4%
Abdominal pain	6%	6%	3%

*Metoclopramide/dexamethasone; phenothiazines/dexamethasone; dexamethasone; prochlorperazine

Of 1836 patients treated with *Kytril* during Phase II and Phase III studies (doses ranging from 0.25 to 20 mg daily), only 3.2% withdrew secondary to adverse events. In contrast, 5.8% of the patients treated with metoclopramide and dexamethasone withdrew secondary to adverse events while 3.7% of the placebo recipients withdrew because of adverse events.[7] The incidences of serious adverse events were 2.7%, 2.5% and 2.2% in the patients who received *Kytril*, metoclopramide plus dexamethasone and placebo, respectively. These serious adverse events included fever, leukopenia and thrombocytopenia, none of which were considered to be related to *Kytril* therapy.[7]

Overdosage

There were no cases of overdosage with oral *Kytril* during clinical trials. Yet, doses of up to 10 mg bid x 7 days were utilized in some studies, without any apparent change in the incidence or severity of adverse events.[7]

Special Populations

Elderly

Of the 1714 patients who received oral *Kytril* alone, 17% were at least 65 years of age or older. The overall rate of adverse events was similar in the elderly patients (60%) as in those who were less than 65 years of age (62%). Although diarrhea was more common in elderly subjects, headache was more common in patients less than 65 years of age. In either case, these events were generally of a mild to moderate intensity. No significant differences in laboratory values were noted between elderly and younger patients.[7]

Hepatically Impaired Patients

Patients with hepatic impairment (defined as liver function tests at least twice the upper limit of normal) represented 4.3% of the 1714 patients who received oral *Kytril* alone. Once again, the rates of adverse events in these patients did not differ significantly from patients with normal liver function tests (62% in each group). Fever, liver function test abnormalities and anemia were more common in the hepatically impaired patients; however, these events were most likely a reflection of the underlying hepatic disorder.[7]

Summary

Kytril Tablets are safe and effective for the prevention of nausea and vomiting associated with emetogenic cancer therapy. The recommended regimen for *Kytril* Tablets is two 1 mg tablets given on the days of chemotherapy. The first tablet should be given up to 1 hour prior to chemotherapy, and the second tablet should be taken 12 hours after the first. No dosage adjustment is recommended for the elderly or for patients with renal or hepatic impairment.[13] The most commonly reported adverse events associated with the use of *Kytril* Tablets were headache and constipation.

We appreciate your interest in *Kytril* Tablets. Please consult the enclosed prescribing information before initiating therapy in your patients. If you have any further questions regarding our products or would like a copy of any of the referenced publications, please contact the Product Information Department at 1-800-366-8900, ext. 5231.

Sincerely,

Thomas G. Cantu, Pharm.D.
Senior Drug Information Product Specialist
Gastrointestinal/Rheumatology Group
Product Information Department
Product Professional Services

Carl J. Friedman, M.D.
Group Director
GI and Metabolism,
Clinical Research, Development
and Medical Affairs, N.A.

TGC\CJF:jsm
Encls:

References:

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13. *Kytril* (granisetron hydrochloride, SmithKline Beecham Pharmaceuticals) Tablets Prescribing Information, Mar 1995.

14. *Kytril* (granisetron hydrochloride, SmithKline Beecham Pharmaceuticals) Injection Prescribing Information, Aug 1994.

Encls: KRL 0

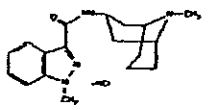
KY-L1T 5011-US

PRESCRIBING INFORMATION 000059

KYTRIL®
granisetron hydrochloride
Tablets

DESCRIPTION

Kytril Tablets contain granisetron hydrochloride, an antinauseant and antiemetic agent. Chemically it is endo-N-(9-methyl-9-azabicyclo [3.3.1] non-3-yl)-1-methyl-1H-indazole-3-carboxamide hydrochloride with a molecular weight of 348.9 (312.4 free base). Its empirical formula is $C_{18}H_{24}N_4O \cdot HCl$, while its chemical structure is:



granisetron hydrochloride

Granisetron hydrochloride is a white to off-white solid that is readily soluble in water and normal saline at 20°C.

Tablets for Oral Administration: Each white, triangular, biconvex, film-coated *Kytril* tablet contains 1.12 mg granisetron hydrochloride equivalent to granisetron, 1 mg. Inactive ingredients are: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate and titanium dioxide.

CLINICAL PHARMACOLOGY

Granisetron is a selective 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT$_1$; 5-HT$_{1A}$; 5-HT$_{1B}$; 5-HT$_2$; for alpha$_1$-, alpha$_2$-, or beta-adrenoreceptors; for dopamine-D$_2$; or for histamine-H$_1$; benzodiazepine; picrotoxin, or opioid receptors.

Serotonin receptors of the 5-HT$_3$ type are located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy that induces vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT$_3$ receptors. This evokes vagal afferent discharge, inducing vomiting. Animal studies demonstrate that, in binding to 5-HT$_3$ receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin. In the ferret animal model, a single granisetron injection prevented vomiting due to high-dose cisplatin or arrested vomiting within 5 to 30 seconds.

In most human studies, granisetron has had little effect on blood pressure, heart rate or ECG. No evidence of an effect on plasma prolactin or aldosterone concentrations has been found in other studies.

Following single and multiple oral doses, *Kytril* slowed colonic transit in normal volunteers. However, *Kytril* had no effect on oro-cecal transit time in normal volunteers when given as a single intravenous (IV) infusion of 50 mcg/kg or 200 mcg/kg.

Pharmacokinetics

In healthy volunteers and adult cancer patients undergoing chemotherapy, administration of oral *Kytril* produced the following mean pharmacokinetic data:

Table 1. Pharmacokinetic Parameters (Median [range]) Following Oral Kytril (granisetron hydrochloride)

	Peak Plasma Concentration [ng/mL]	Terminal Phase Plasma Half-Life (h)	Volume of Distribution [L/kg]	Total Clearance [L/h/kg]
Cancer Patients 1.0 mg b.i.d., 7 days (n=27)	5.99 [0.62 to 30.9]	N.D.*	N.D.	0.52 [0.09 to 7.37]
Volunteers single 1.0 mg dose (n=38)	3.63 [0.27 to 9.14]	6.73 [0.96 to 19.5]	3.94 [1.85 to 28.4]	0.48 [0.11 to 24.5]

* Not determined after oral administration; following a single intravenous dose of 40 mcg/kg, terminal phase half-life was determined to be 8.95 hours.

N.D. Not determined

The effects of gender on the pharmacokinetics of oral *Kytril* have not been studied. However, after intravenous infusion of *Kytril*, no difference in mean AUC was found between males and females, although males had a higher C_{max} generally.

When oral *Kytril* was administered with food, AUC was decreased by 5% and C_{max} increased by 30% in non-fasted healthy volunteers who received a single dose of 10 mg.

Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. Animal studies suggest that some of the metabolites may also have 5-HT$_3$ receptor antagonist activity.

Clearance is predominantly by hepatic metabolism. In normal volunteers, approximately 11% of the orally administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 48% in the urine and 38% in the feces.

In vitro liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily.

Plasma protein binding is approximately 65% and granisetron distributes freely between plasma and red blood cells.

In the elderly and in patients with renal failure or hepatic impairment, the pharmacokinetics of granisetron was determined following administration of intravenous *Kytril*.

Elderly: The ranges of the pharmacokinetic parameters in elderly volunteers (mean age 71 years), given a single 40 mcg/kg intravenous dose of *Kytril* injection, were generally similar to those in younger healthy volunteers; mean values were lower for clearance and longer for half-life in the elderly.

Renal Failure Patients: Total clearance of granisetron was not affected in patients with severe renal failure who received a single 40 mcg/kg intravenous dose of *Kytril* injection.

Hepatically Impaired Patients: A pharmacokinetic study with intravenous *Kytril* in patients with hepatic impairment due to neoplastic liver involvement showed that total clearance was approximately halved compared to patients without hepatic impairment. Given the wide variability in pharmacokinetic parameters noted in patients and the good tolerance of doses well above the recommended 1.0 mg b.i.d. dose, dosage adjustment in patients with possible hepatic functional impairment is not necessary.

Pediatrics: The pharmacokinetics of granisetron has not been adequately studied in children.

CLINICAL TRIALS

Oral *Kytril* prevents nausea and vomiting associated with emetogenic cancer therapy as shown by 24-hour efficacy data from three double-blind studies. The first trial compared oral *Kytril* doses of 0.25 to 2.0 mg b.i.d., in 930 cancer patients receiving, principally, cyclophosphamide, carboplatin and cisplatin (20 mg/m^2 to 50 mg/m^2). Efficacy was based on: complete response (i.e., no vomiting, no moderate or severe nausea, no rescue medication), no vomiting and no nausea. Table 2 summarizes the results of this study.

Table 2. Prevention of Nausea and Vomiting 24 Hours Post-Chemotherapy[1]

	Percentages of Patients Oral *Kytril* Dose			
Efficacy Measures	0.25 mg b.i.d. (n=229) %	0.5 mg b.i.d. (n=228) %	1.0 mg b.i.d. (n=233) %	2.0 mg b.i.d. (n=220) %
Complete Response[2]	61	70*	81*†	72*
No Vomiting	66	77*	88*	79*
No Nausea	48	57	63*	54

1. Chemotherapy included oral and injectable cyclophosphamide, carboplatin, cisplatin (20 mg/m^2 to 50 mg/m^2), doxorubicin, daunorubicin, epirubicin.
2. No vomiting, no moderate or severe nausea, no rescue medication.
* Statistically significant ($P \leq 0.011$) vs. 0.25 mg b.i.d.
† Statistically significant ($P \leq 0.011$) vs. 0.5 mg b.i.d.

A second double-blind, randomized trial compared oral *Kytril* 1.0 mg b.i.d. with prochlorperazine sustained release capsules 10.0 mg b.i.d., in 230 cancer patients receiving moderately emetogenic chemotherapeutic agents. Oral *Kytril* was significantly better than prochlorperazine in preventing nausea and vomiting (see Table 3).

Table 3. Prevention of Nausea and Vomiting 24 Hours Post-Chemotherapy[1]

	Percentages of Patients Antiemetic Regimen	
Efficacy Measures	*Kytril* 1.0 mg b.i.d. (n = 119) %	Prochlorperazine 10.0 mg b.i.d. (n=111) %
Complete Response[2]	74*	41
No Vomiting	82*	48
No Nausea	58*	35

1. Chemotherapy included injectable cyclophosphamide, carboplatin, cisplatin (20 mg/m^2 to 50 mg/m^2), doxorubicin, daunorubicin, epirubicin.
2. No vomiting, no moderate or severe nausea, no rescue medication.
* Statistically significant ($P \leq 0.001$) vs. prochlorperazine.

A third double-blind trial compared oral *Kytril* 1.0 mg b.i.d., relative to placebo (historical control), in 119 cancer patients receiving high-dose cisplatin (mean dose 80 mg/m^2). At 24 hours, oral *Kytril* 1.0 mg b.i.d. was significantly ($P \leq 0.001$) superior to placebo (historical control) in all efficacy parameters: complete response (52%), no vomiting (58%) and no nausea (45%). The placebo rates were 7%, 14% and 7%, respectively, for the three efficacy parameters.

No controlled study comparing granisetron injection with the oral formulation to prevent chemotherapy-induced nausea and vomiting has been performed.

INDICATIONS AND USAGE

Kytril (granisetron hydrochloride) is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.

CONTRAINDICATIONS

Kytril is contraindicated in patients with known hypersensitivity to the drug or any of its components.

PRECAUTIONS

Drug Interactions

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system. There have been no definitive drug-drug interaction studies to examine pharmacokinetic or pharmacodynamic interaction with other drugs but, in humans, *Kytril* injection has been safely administered with drugs representing benzodiazepines, neuroleptics and anti-ulcer medications commonly prescribed with antiemetic treatments. *Kytril* injection also does not appear to interact with emetogenic cancer chemotherapies. Because granisetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of granisetron.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, rats were treated orally with granisetron 1, 5 or 50 mg/kg/day (6, 30 or 300 mg/m^2/day). The 50 mg/kg/day dose was reduced to 25 mg/kg/day (150 mg/m^2/day) during week 59 due to toxicity. For a 50 kg person of average height (1.46m^2 body surface area), these doses represent 6, 20 and 101 times the recommended clinical dose (1.48 mg/m^2, oral) on a body surface area basis. There was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in males treated with 5 mg/kg/day (30 mg/m^2/day, 20 times the recommended human dose based on body surface area) and above, and in females treated with 25 mg/kg/day (150 mg/m^2/day, 101 times the recommended human dose based on body surface area). No increase in liver tumors was observed at a dose of 1 mg/kg/day (6 mg/m^2/day, 4 times the recommended human dose based on body surface area) in males and 5 mg/kg/day (30 mg/m^2/day, 20 times the recommended human dose based on body surface area) in females. In a 12-month oral toxicity study, treatment with granisetron 100 mg/kg/day (600 mg/m^2/day, 405 times the recommended human dose based on body surface area) produced hepatocellular adenomas in male and female rats while no such

tumors were found in the control rats. A 24-month [illegible] mouse carcinogenicity study of granisetron did not show a statistically significant increase in tumor incidence, but the study was not conclusive.

Because of the tumor findings in rat studies, Kytril (granisetron hydrochloride) Tablets should be prescribed only at the dose and for the indication recommended (see INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION).

Granisetron was not mutagenic in *in vitro* Ames test and mouse lymphoma cell forward mutation assay, and *in vivo* mouse micronucleus test and *in vitro* and *ex vivo* rat hepatocyte UDS assays. It, however, produced a significant increase in UDS in HeLa cells *in vitro* and a significant increased incidence of cells with polyploidy in an *in vitro* human lymphocyte chromosomal aberration test.

Granisetron at oral doses up to 100 mg/kg/day (600 mg/m²/day, 405 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects. Pregnancy Category B. Reproduction studies have been performed in pregnant rats at oral doses up to 125 mg/kg/day (750 mg/m²/day, 507 times the recommended human dose based on body surface area) and pregnant rabbits at oral doses up to 32 mg/kg/day (378 mg/m²/day, 255 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to granisetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether granisetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when *Kytril* is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

During clinical trials, 325 patients 65 years of age or older received oral *Kytril*: 238 were 65 to 74 years of age and 27 were 75 years of age or older. Efficacy and safety were maintained with increasing age.

ADVERSE REACTIONS

Over 2,800 patients have received oral *Kytril* in clinical trials with emetogenic cancer therapies consisting primarily of cyclophosphamide or cisplatin regimens.

In patients receiving oral *Kytril* 1 mg b.i.d. for 1, 7 or 14 days, the following table lists adverse experiences reported in more than 5% of the patients with comparator and placebo incidences.

Table 4. Principal Adverse Events in Clinical Trials

	Percent of Patients with Event		
	Oral *Kytril*[1] 1 mg b.i.d. (n=978)	Comparator[2] (n=689)	Placebo (n=185)
Headache[3]	21%	13%	12%
Constipation	18%	16%	9%
Asthenia	14%	10%	4%
Diarrhea	8%	10%	4%
Abdominal pain	6%	6%	3%

1. Adverse events were recorded for 7 days when oral *Kytril* was given on a single day and for up to 28 days when oral *Kytril* was administered for 7 or 14 days.
2. Metoclopramide/dexamethasone; prochlorperazine; dexamethasone alone; prochlorperazine.
3. Usually mild to moderate in severity.

Other adverse events reported in clinical trials were:

Gastrointestinal: In single-day dosing studies in which adverse events were collected for 7 days, nausea (15%) and vomiting (9%) were recorded as adverse events after the 24-hour efficacy assessment period.

Hepatic: In comparative trials, elevation of AST and ALT (>2 times the upper limit of normal) following the administration of oral *Kytril* occurred in 5% and 6% of patients, respectively. These frequencies were not significantly different from those seen with comparators (AST: 2%; ALT: 9%).

Cardiovascular: Hypertension (1%), hypotension, angina pectoris, atrial fibrillation and syncope have been observed rarely.

Central Nervous System: Dizziness (3%), insomnia (3%), anxiety (2%), somnolence (1%). One case compatible with but not diagnostic of extrapyramidal symptoms has been reported in a patient treated with oral *Kytril*.

Hypersensitivity: Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis, shortness of breath, hypotension, urticaria) have been reported.

Other: Fever (5%). Events often associated with chemotherapy also have been reported: leukopenia (11%), decreased appetite (5%), anemia (4%), alopecia (3%), thrombocytopenia (3%).

Over 5,000 patients have received injectable *Kytril* in clinical trials.

Table 5 gives the comparative frequencies of the five commonly reported adverse events (≥3%) in patients receiving *Kytril* injection, 40 mcg/kg, as single-day chemotherapy trials. These patients received chemotherapy, primarily cisplatin, and intravenous fluids during the 24-hour period following *Kytril* injection administration.

Table 5. Principal Adverse Events in Clinical Trials—Single-Day Chemotherapy

	Percent of Patients with Event	
	Kytril Injection[1] 40 mcg/kg (n=1,268)	Comparator[2] (n=422)
Headache	14%	6%
Asthenia	5%	6%
Somnolence	4%	15%
Diarrhea	4%	6%
Constipation	3%	3%

1. Adverse events were generally recorded over 7 days post-*Kytril* injection administration.
2. Metoclopramide/dexamethasone and prochlorperazine/dexamethasone.

In the absence of a placebo group, there is uncertainty as to how many of these events should be attributed to *Kytril*, except for headache which was clearly more frequent than in comparison groups.

OVERDOSAGE

There is no specific treatment for granisetron hydrochloride overdosage. In case of overdosage, symptomatic treatment should be given. Overdosage of up to 38.5 mg of granisetron hydrochloride injection has been reported without symptoms. Any the occurrence of a slight headache.

DOSAGE AND ADMINISTRATION

The recommended adult dosage of oral *Kytril* (granisetron hydrochloride) is 2 mg twice daily. The first 1 mg tablet is given up to 1 hour before chemotherapy, and the second tablet, 12 hours after the first, only on the day(s) chemotherapy is given. Continued treatment, while not on chemotherapy, has not been found to be useful.

Use in the Elderly, Renal Failure Patients or Hepatically Impaired Patients: No dosage adjustment is recommended. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

Pediatric Use: Data on oral *Kytril* are not available.

HOW SUPPLIED

Tablets: White, triangular, biconvex, film-coated tablets debossed K1 on one face; 1 mg in Unit-of-Use Packages of 2; in Single Unit Packages of 20 (intended for institutional use only).

1 mg Unit-of-Use 2's: NDC 0029-4151-39
1 mg SUP 20's: NDC 0029-4151-05

Store between 15° and 30°C (59° and 86°F). Protect from light.

DATE OF ISSUANCE MAR. 1995

Manufactured in Crawley, UK, by
SmithKline Beecham Pharmaceuticals
for SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

KYTLIT

580059

Kytril 1mg vial (1mg/mg)

	Cost	Reimbursement	Profit
(1mg)	113.00	166 (AWP)	$53 —
(.7mg)	($113 x .7) $79.10	166 (AWP)	$86.90

Zofran 4mg vial

	Cost ($169)	Reimbursement	Profit
(32mg)	($169 x 80%) 135.20	($5.40 x 32) 172.80	37.60

HIGHLY CONFIDENTIAL

SB
SmithKline Beecham
Pharmaceuticals

Michael J. Di Bartolomeo
Senior Pharmaceutical Consultant

2460 Waltham, Troy, MI 48098
Telephone (810) 528 2476 Beeper (810) 400 9527

GSK-MDL-KY03
000220

Efficacy Of *KYTRIL* Tablets at 24 Hours

Compared To *KYTRIL* IV and Zofran IV

Drug Regimen	Dose	Total Control	Cisplatin Dose (mg/m^2)	Study
Kytril tablets	1 mg BID	44%	81	022
Kytril IV	10 µg/kg	38%	81.5	251
Zofran IV	0.15 mg/kg (0,4,8 hrs)	39%	81.5	251

HIGHLY CONFIDENTIAL

GSK-MDL-KY03 002221

5-HT3 Comparison
Adverse Drug Reactions

Reaction	Granisetron	Ondansetron
	n = 1,268	n = 547
Headache	14%	17%
Diarrhea	4%	16%
Fever	3%	8%
Constipation	3%	11%
Increased LFT's	3%	1-2%

Reference: Zofran and Kytril Package Inserts

HIGHLY CONFIDENTIAL

Pharmacokinetic Comparison

Granisetron versus Ondansetron

Parameter	Ondansetron	Granisetron
Half-Life		
Normal	3.5 hours	5 hours
Cancer	4 hours	9 hours
Peds	2.4 hours	
Metabolism	Hepatic	Hepatic
Clearance	Decreased in liver impairment; Increased in peds	Decreased in liver impairment
Bioavailability	56%	

GSK- MDL- KYO3
000223

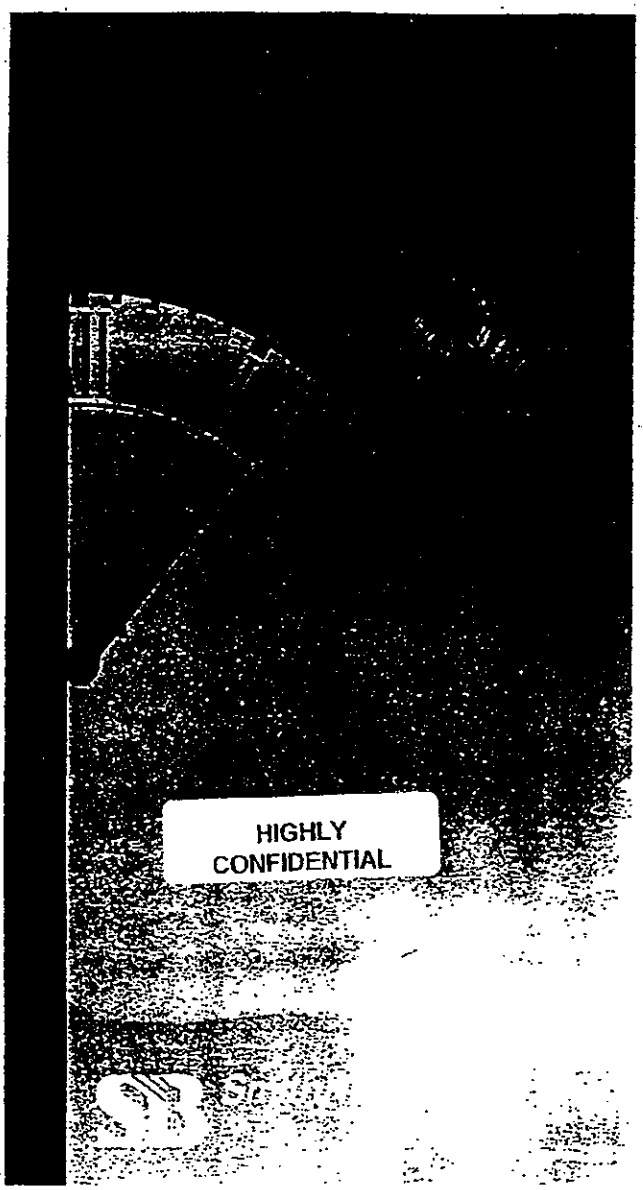
EXHIBIT B

SYMPOSIUM HIGHLIGHTS

BULLETIN

THERAPEUTIC CONSIDERATIONS FOR ANTIEMETIC THERAPY IN ONCOLOGY PATIENTS

Highlights of a symposium, sponsored by SmithKline Beecham Pharmaceuticals, which was held December 7, 1994, at the American Society of Health-System Pharmacists Midyear Clinical Meeting in Miami Beach, Florida



PROGRAM FACULTY:
Michael Gosland, PharmD
Assistant Professor
University of Kentucky
College of Pharmacy and Medicine
Lucille P. Markey Cancer Center

Symposium Highlights

- Nausea and vomiting are the most feared treatment-related side effects of cancer chemotherapy.
- Suboptimal antiemetic therapy can result in physical and psychological complications and reduced quality of life.
- Factors have been identified that place patients at high risk for emesis.
- The emetogenic potential of chemotherapeutic agents increases with combination therapies and high-dose regimens.
- Pharmacokinetic differences between granisetron and ondansetron exist, but clinical significance has not yet been determined.
- The pharmacodynamic differences between granisetron and ondansetron have been well characterized in several pre-clinical models. These differences may become important when dose reductions of 5-HT_3-receptor antagonists are evaluated in the clinical setting.
- Granisetron doses above 10 μg/kg do not result in improved efficacy.
- Oral administration of 5-HT_3-receptor antagonists may offer clinical and economic benefits.
- 5-HT_3-receptor antagonists should be used only for acute chemotherapy-induced nausea and vomiting.
- The combination of a corticosteroid plus a 5-HT_3-receptor antagonist results in improved efficacy and reduced cost.

Introduction

According to a 1983 study,[1] nausea and vomiting are the two most feared chemotherapy-related side effects in patients with cancer, surpassing even hair loss, going to treatments, treatment duration, and hypodermic injection, explained Michael P. Gosland, PharmD, Assistant Professor at the University of Kentucky College of Pharmacy and Medicine and the Lucille P. Markey Cancer Center. The 5-HT_3-receptor antagonists have revolutionized the prevention of chemotherapy-induced nausea and vomiting and are freeing many patients from these two important side effects.

These and other issues were discussed by Dr. Gosland during a symposium entitled "Therapeutic Considerations for Antiemetic Therapy in Oncology Patients" that was held on December 7, 1994 during the American Society of Health-System Pharmacists Midyear Clinical Meeting in Miami Beach, Florida. This Highlights Bulletin summarizes the most important points made by Dr. Gosland.

Consequences of Suboptimal Antiemetic Therapy

According to Dr. Gosland, an important part of the management of the patient undergoing cancer chemotherapy is control of nausea and vomiting. The consequences of suboptimal antiemetic therapy can be debilitating and can adversely affect cancer treatment. Physical consequences include dehydration, electrolyte imbalance, and accelerated weight loss. Anticipatory emesis, loss of confidence in the treatment and in care givers, and noncompliance with further chemotherapy are among the psychological consequences. These physical and psychological effects can negatively impact quality of life.

Considerations for Antiemetic Therapy

Factors that need to be considered in the prevention of chemotherapy-induced nausea and vomiting include patient-specific risk factors and the emetic potential of the individual chemotherapeutic agent. In general, younger patients and females are at greater risk of chemotherapy-induced emesis than older patients or males. Individuals who do not drink alcoholic beverages are also at higher risk for emesis, as are patients with a prior history of poor emetic control, motion sickness, and emesis during pregnancy.

Along with these patient-specific risk factors, the chemotherapeutic agent also plays an important role in the risk of emesis.

Emetogenic Potential of Selected Chemotherapeutic Agents

Chemotherapy is generally categorized from high to low emetogenic potential based on the incidence of emesis observed if no antiemetics are used. Cisplatin, for example, is categorized as highly emetogenic and 90% of patients will develop emesis if no antiemetic therapy is given. In contrast, vincristine has a low emetogenic potential with less than 10% of patients developing emesis. The emetogenic potential of various chemotherapeutic agents is summarized in Table 1. This table depicts the emesis potential based on individual drugs, however, most chemotherapeutic agents are administered in combination regimens. When combining agents, it is important to base the emetogenic potential on the most emetogenic agent administered. If a regimen consists of two moderately emetogenic agents administered concomitantly, such as cyclophosphamide (400 to 599 mg/M²) with doxorubicin (40 mg/M²) for the treatment of breast cancer, the combined regimen is actually moderately highly emetogenic and may require more aggressive antiemetic therapy. Finally, emetogenic potential also is dose-related. For example, although cisplatin generally is considered highly emetogenic, doses ranging from ≥ 20 mg/M² to ≤ 50 mg/M² are actually moderately emetogenic.

These considerations are particularly important when using antiemetics for the bone marrow transplantation population, in which dose-intensive chemotherapy is used. These guidelines of emetogenic potential can help the clinician when prescribing antiemetics. When using those agents classified as having moderately low emetogenic potential, aggressive antiemetic therapy with 5-HT_3-receptor antagonists is generally not needed. Antiemetics often are not needed at all in those patients receiving agents having low emetogenic potential.

High (>90%)	Moderately High (60% to 90%)	Moderate (30% to 60%)	Moderately Low (10% to 30%)	Low (<10%)
Cisplatin	Carmustine	5-Fluorouracil	Bleomycin	Busulfan
Dacarbazine	Lomustine	Doxorubicin	Hydroxyurea	Chlorambucil
Mechlorethamine	Cyclophosphamide	Daunorubicin	Melphalan	Thioguanine
Streptozocin	Dactinomycin	Asparaginase	Etoposide	Vincristine
Cytarabine (>500 mg/m²)	Plicamycin	Mitomycin	Cytarabine	Estrogens
	Procarbazine	Altretamine	Methotrexate	Progestins
	Methotrexate (>200 mg/m²)		Thiotepa	Corticosteroids
			Vinblastine	Androgens

Table 1. Emetogenic Potential of Chemotherapeutic Agents[2] (adapted with permission)

5-HT_3-Receptor Antagonists

The 5-HT_3-receptor antagonists block serotonin receptors on vagal afferent nerves in the gastrointestinal tract and at the chemoreceptor trigger zone located in the area postrema. Two 5-HT_3-receptor antagonists are commercially available (ondansetron HCL, Zofran®, Cerenex; granisetron HCL, Kytril®, SmithKline Beecham) and others are undergoing clinical investigation (eg, tropisetron, dolasetron). The side effects associated with most 5-HT_3-receptor antagonists are mild and include diarrhea, headache, sedation, dizziness, and xerostomia. Although the half-lives of granisetron (9 hours) and ondansetron (4 hours) in cancer patients are substantially different, the significance of this has not been demonstrated in clinical trials. Both drugs are usually administered as a single, one-time dose prior to chemotherapy. While the clinical significance of the pharmacokinetic differences between ondansetron and granisetron have yet to be determined, the pharmacodynamic differences between the two agents may be important in some situations.

Pre-clinical pharmacology studies using the ferret model have shown that granisetron follows a linear dose-response curve, whereas ondansetron follows a nonlinear pattern.[3] With granisetron, as the dose increases, there is a linear decrease in the mean number of episodes of chemotherapy-induced emesis. In the ferret, ondansetron initially reduced the number of vomits, then as the dose of ondansetron was escalated, an increase in emesis was observed before the emetic response was totally abolished. The ondansetron nonlinear dose-response relationship may become a problem depending on the dose of ondensetron used and the concentration of ondansetron achieved. While this phenomenon is not observed at the currently approved dose (ie, 32 mg), with the practice of "down-dosing" ondansetron, inadequate control of chemotherapy-induced emesis may occur. Well controlled clinical trials are needed to adequately assess the efficacy of ondansetron dose reductions.

Dr. Gosland reviewed recent research documenting the lack of improvement in therapeutic response with granisetron doses in excess of 10 μg/kg. Granisetron doses of 5, 10, 20 and 40 μg/kg were evaluated in 184 patients treated with a highly emetogenic regimen (mean cisplatin dose of 98 mg/M² with or without other chemotherapeutic agents).[4] The complete response rate (defined as no vomiting or retching and no use of rescue medications) was 18% at the 5 μg/kg dose, 41% at the 10 μg/kg dose, 40% at the 20 μg/kg dose, and 47% at the 40 μg/kg dose. Nausea-free response was seen in 15% of patients at the 5 μg/kg dose and in 35%, 38%, and 43% of patients at the 10, 20, and 40 μg/kg doses, respectively. Statistically significant differences in acute nausea and vomiting control were observed between the 5 μg/kg and 10 μg/kg, and the 20 μg/kg and 40 μg/kg doses. There were no significant differences between the 10 μg/kg dose and the 20 μg/kg and 40 μg/kg doses.

Benefits of Oral Therapy with 5-HT_3-Receptor Antagonists

According to Dr. Gosland, oral administration of 5-HT_3-receptor antagonists may offer clinical and economic advantages relative to intravenous administration. The economic advantage is derived from the greater ease of administering an oral versus a parenteral product and the improved clinical response associated with the oral product. The improved clinical response may be due to the direct effects of the 5-HT_3-receptor antagonists on serotonin receptors in the gut.

The use of oral ondansetron at doses of 4 to 8 mg TID has been limited primarily to the control of emesis in the moderately emetogenic chemotherapy regimens. Complete response rates (no emesis or rescue medications needed) of 65%[5,6] have been achieved. A similar response is seen with moderately emetogenic chemotherapy regimens using oral granisetron at a dose of 1 mg BID.[7]

A recent study with oral granisetron by Heron and colleagues[8] demonstrated that oral granisetron may also be effective in the prevention of nausea and vomiting associated with highly emetogenic chemotherapy. In this study, 357 patients receiving cisplatin-containing chemotherapy (mean dose 81 mg/M²) were randomized to either oral granisetron alone (1 mg BID), oral granisetron (1 mg BID) with dexamethasone (12 mg x 1 dose prior to chemotherapy), or dexamethasone (12 mg x 1 dose prior to chemotherapy) with high-dose metoclopramide (8 hour infusion of 4 mg/kg followed by 10 mg orally TID). The complete response rate (no nausea or vomiting during the first 24 hours) was 37.5% in the metoclopramide plus dexamethasone group, 43.7% in patients treated with granisetron alone, and 54.7% in patients treated with granisetron plus dexamethasone. There was a statistically significant benefit with the combination of oral granisetron and dexamethasone versus the other two therapies. This study was unique in that the data were analyzed based on certain patient populations with risk factors for emesis. They found that patients under the age of 45 years and females had a significantly higher overall rate of chemotherapy-induced emesis compared to other groups.

These high risk patients also benefited the most from the granisetron and dexamethasone therapy. This study showed that an oral antiemetic can be used to prevent acute nausea and vomiting associated with cisplatin. Although more research is needed in this area, oral 5-HT_3-receptor antagonists may offer an economic and therapeutic advantage in the prevention of chemotherapy-induced acute nausea and vomiting.

Considerations for Analysis of Antiemetic Research

Dr. Gosland suggested that caution be exercised when comparing efficacy results among clinical trials because the response criteria used may differ. Both nausea and vomiting should be assessed when evaluating antiemetic efficacy. However, some investigators

report vomiting episodes only, while others report both the degree of nausea and the number of vomiting episodes when grading the response to 5-HT_3-receptor antagonists (Table 2).

5-HT_3-receptor antagonists are highly effective in the prevention of chemotherapy-induced acute nausea and vomiting, however, controlled clinical trials do not support the use of these agents in patients who develop emesis or in the prevention of delayed nausea and vomiting. Therefore, these agents should only be used in the prevention of acute nausea and vomiting associated with chemotherapy.

Delayed nausea and vomiting occurs more than 24 hours after chemotherapy administration, whereas acute effects occur less than 24 hours after chemotherapy. Most often, delayed effects consist primarily of nausea and not vomiting. Treatment for delayed nausea can include dopamine antagonists (eg, prochlorperazine or metoclopramide) and corticosteroids (eg, dexamethasone).

Cost-Effectiveness of Antiemetic Therapy

Cost-effectiveness is of growing importance in formulary decisions. Cost-effectiveness considers not only the cost of the drugs used in managing nausea and vomiting, but the costs associated with inadequate control. For example, despite the increase in the cost of drug, the addition of dexamethasone to ondansetron results in improved cost-effectiveness because of improved outcomes (ie, control of nausea and vomiting) compared with the use of ondansetron alone.[11] Dexamethasone has also been shown to improve outcomes when used with granisetron.[11] The comparative cost-effectiveness of granisetron and ondansetron was evaluated at the University of Kentucky Lucille P. Markey Cancer Center. The results showed that both agents were equally effective in the prevention of emesis associated with moderately-highly as well as highly emetogenic chemotherapy regimens. When the analyses included the cost of the initial antiemetic agents used, as well as any rescue antiemetics used, the results revealed that granisetron (10 μg/kg) was more cost-effective than ondansetron (32 mg).

Summary

In conclusion, Dr. Gosland stated that "5-HT_3-receptor antagonists have revolutionized the prevention of chemotherapy-induced nausea and vomiting and that more well-controlled trials are needed to compare the cost-effectiveness of these agents." ■

Table 2. Efficacy Assessment in Clinical Trials with 5-HT_3-Receptor Antagonists[9] (adapted with permission)

Response	Granisetron	Ondansetron
Complete	No vomiting and no or mild nausea	No emetic episodes
Major	1 episode of vomiting or moderate to severe nausea	1 to 2 emetic episodes
Minor	2 to 4 vomits	3 to 5 emetic episodes
Failure	> 4 vomits	> 5 emetic episodes

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